Susan Hanley

Considered 9/28/02

Access DB# 63098

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: My-Chau Tran Examiner #: 78933 Date: 3/25/02
Art Unit: 1641 Phone Number 30 5-6999 Serial Number: 09/849,781
Mail Box and Bldg/Room Location: CM1, 8A16 Results Format Preferred (circle): PAPER DISK E-MAIL
7E12

If more than one search is submitted, please prioritize searches in order of need.

****

Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Protein chips for high throughput screening of protein activity

Inventors (please provide full names): Michael Snyder; Mark Reed; Heng Zhu; James Frank Klemic

Earliest Priority Filing Date: 5/04/2000

For Sequence Searches Only *Please include all pertinent information (parent, child, divisional, or issued patent numbers) along with the appropriate serial number.*

RECEIVED MAR 25 2002 (STIC)

Mrs. Hanley,

Can you please perform the following searches:

1) Inventors search
2) Attached claim with the following keywords:
   a) proteins (expressed)
   b) casting
   c) mold and secondary
   d) 3-glycidooxypropyl trimethyoxysilane
   e) lymphocyte activation
   f) chemenic
   g) mitogen
   h) protein chip w/ PY < 2000.

Thank-you

Point of Contact:
Susan Hanley
Technical Info. Specialist
CM1 6B05 Tel: 305-4053

****

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=> d his l1-l69

     (FILE 'HOME' ENTERED AT 17:47:41 ON 03 APR 2002)

     FILE 'HCAPLUS' ENTERED AT 17:47:48 ON 03 APR 2002
L1           376 S SNYDER M?/AU
L2           900 S REED, M?/AU
L3          2685 S ZHU H?/AU
L4            10 S KLEMIC J?/AU
L5          3957 S L1-4
L6             2 S L5 AND  PROTEIN CHIP
                 SELECT RN L6 1-2

     FILE 'REGISTRY' ENTERED AT 17:49:09 ON 03 APR 2002
L7            20 S E1-20

     FILE 'HCAPLUS' ENTERED AT 17:49:15 ON 03 APR 2002
L8             2 S L6 AND L7
L9            88 S PROTEIN CHIP
L10        21937 S HIGH DENSITY
L11          850 S L10(5A)(PROTEIN OR CELL?)
L12      2371093 S ARRAY OR SOLID SUPPORT OR POLYMER OR ?SILAN? OR ?SILOX? OR ?S
L13          110 S L11 AND L12
L14        86212 S LYMPHOCYTE(3A)ACTIVAT? OR CHEMERIC OR CHIMERIC OR MITOGEN?
L15            2 S L13 AND L14
L16            5 S L9 AND L14
L17            5 S L15-16 NOT L8
L18        53088 S HIGH(4A)(DENSITY OR THROUGH-PUT OR  ?WELL)
L19         6233 S L18(5A)(?PROTEIN OR ?PEPTID? OR ?CELL?)
L20          456 S L19 AND L12
L21            5 S L20 AND L14
L22            4 S L21 NOT L17
L23          173 S L19(P)L12
L24            5 S L23 AND MICROSCOP?
L25            2 S L23 AND SLIDE
L26           10 S L20 AND MICROSCOP?
L27           10 S L24-26
L28            9 S L27 NOT (L21 OR L17)
L29           36 S L9 AND L12
L30            5 S L9 AND L14
L31           43 S L28-30 NOT (L21 OR L17)
L32            4 S L31 AND ?POSITION?
L33           39 S L31 NOT L32
L34            4 S L33 AND ?WELL
L35           39 S L33-34
L36            9 S L35 AND PATENT/DT
L37           30 S L35 NOT L36
L38            7 S L37 AND PY<2000
L39            3 S L36 AND PRD<2000
L40           52 S L9 NOT L29
L41           10 S L40 AND PATENT/DT
L42            3 S L41 AND PRD<2000
L43           42 S L40 NOT L41
L44           14 S L43 AND PY<2000
L45            0 S L44 AND L12

     FILE 'MEDLINE, BIOSIS, WPIDS, USPATFULL' ENTERED AT 18:20:22 ON 03 APR
     2002
L46          160 S PROTEIN CHIP
L47       394201 S HIGH(4A)(DENSITY OR THROUGH-PUT OR  WELL OR MICROWELL OR THRO
```

- inventor search

2 cites w/ 20 compounds displayed

5 cites

4 cites

7 cites

3 cites

3 cites

PY = publication year for journal articles

PRD = priority date for patents

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L48       68186 S L47(5A)(?PROTEIN OR ?PEPTID? OR ?CELL?)
L49        1551 S (L46 OR L48)(10A)(ARRAY OR ASSAY? OR DIAGNOS? OR SLIDE OR MIC
L50         536 S L49 AND (SOLID SUPPORT OR POLYMER OR ?SILAN? OR ?SILOX? OR ?S
L51           1 S L50 AND "PER CM2"
L52           1 S L50 AND "WELLS/CM2"
L53         434 S L50 AND AREA
L54     1107363 S LYMPHOCYTE(3A)ACTIVAT? OR MITOGEN? OR ANTIGEN? OR CH!MERIC
L55          53 S L53 AND L54
L56      303870 S SURFACE AREA
L57         153 S L56 AND L50
L58          26 S L57 AND L54
L59          26 S L58 NOT L51
L60          26 DUP REM L59 (0 DUPLICATES REMOVED)

     FILE 'USPATFULL' ENTERED AT 18:37:39 ON 03 APR 2002
L61          26 S L59
L62          14 S L61 AND PRD<2000
L63           5 S PROTEIN CHIP/CLM
L64          42 S PROTEIN CHIP
L65          22 S L64 (P)(ARRAY OR WELL OR MICROWELL OR SOLID SUPPORT OR MATRI
L66          19 S L65 AND POSITION?
L67          17 S L66 AND (SURFACE AREA OR CONCENTRATION OR "PER CM2" OR "WELL
L68          17 S L67 NOT L62
L69           4 S L68 AND PRD<2000
```

1 cite appl. work L51 & L52 are same cite

14 ~~cite~~ patents

4 patents

Inventa Search

TRAN 09/849,781

=> d ibib abs hitstr 1

L8 ANSWER 1 OF 2 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:816983 HCAPLUS
DOCUMENT NUMBER: 135:354956
TITLE: High density protein arrays for screening of protein activity
INVENTOR(S): **Snyder, Michael; Reed, Mark; Zhu, Heng; Klemic, James Frank**
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

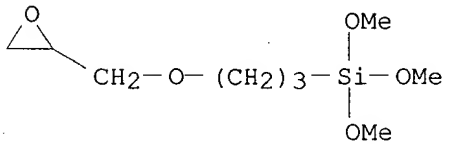
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083827	A1	20011108	WO 2001-US14526	20010504

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-201921P P 20000504
US 2000-221034P P 20000727

AB The invention concerns **protein chips** useful for the large-scale study of protein function where the chip contains densely packed reaction wells. The invention also relates to methods of using **protein chips** to assay simultaneously the presence, amt., and/or function of proteins present in a protein sample or on one **protein chip**, or to assay the presence, relative specificity, and binding affinity of each probe in a mixt. of probes for each of the proteins on the chip. The invention also relates to methods of using the **protein chips** for high d. and small vol. chem. reactions. Also, the invention relates to polymers useful as **protein chip** substrates and methods of making **protein chips**. The invention further relates to compds. useful for the derivatization of **protein chip** substrates.

IT **2530-83-8**, 3-Glycidoxypropyltrimethoxysilane
RL: NUU (Other use, unclassified); USES (Uses)
(as a linker; high d. protein arrays for screening of protein activity)
RN 2530-83-8 HCAPLUS
CN Silane, trimethoxy[3-(oxiranylmethoxy)propyl]- (9CI) (CA INDEX NAME)



IT **16833-27-5**, Oxide

RL: DEV (Device component use); USES (Uses)
(castable; high d. protein arrays for screening of protein activity)
RN 16833-27-5 HCAPLUS
CN Oxide (6CI, 8CI, 9CI) (CA INDEX NAME)

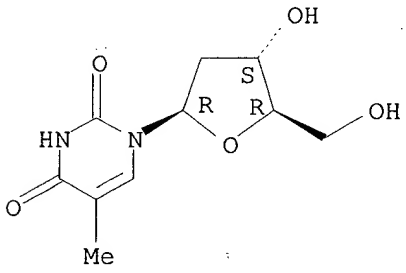
O^{2-}

IT **14392-02-0**, Chromium-51, analysis
RL: ANT (Analyte); ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)
RN 14392-02-0 HCAPLUS
CN Chromium, isotope of mass 51 (8CI, 9CI) (CA INDEX NAME)

^{51}Cr

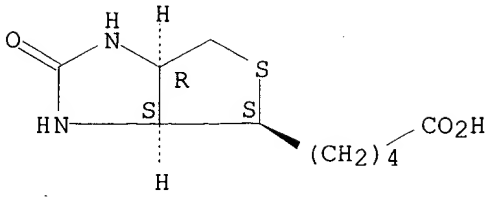
IT **50-88-4**, 3H-Thymidine, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)
RN 50-88-4 HCAPLUS
CN Thymidine, labeled with tritium (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



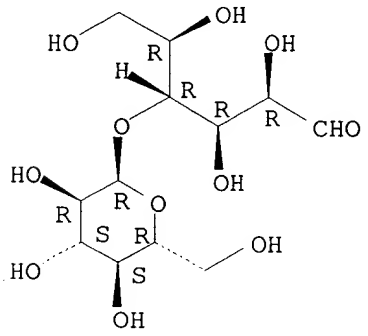
IT **58-85-5**, Biotin **69-79-4**, Maltose **70-18-8**,
Glutathione, uses **7440-02-0**, Nickel, uses **9001-92-7**,
Protease **9002-07-7D**, Trypsin, derivs. **9012-30-0**,
Acetylase **9013-05-2**, Phosphatase **9032-92-2**,
Glycosidase
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)
RN 58-85-5 HCAPLUS
CN 1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



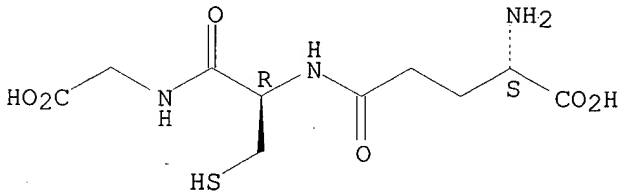
RN 69-79-4 HCAPLUS
CN D-Glucose, 4-O-.alpha.-D-glucopyranosyl- (6CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 70-18-8 HCAPLUS
CN Glycine, L-.gamma.-glutamyl-L-cysteinyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 7440-02-0 HCAPLUS
CN Nickel (8CI, 9CI) (CA INDEX NAME)

Ni

RN 9001-92-7 HCAPLUS
CN Proteinase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9002-07-7 HCAPLUS
CN Trypsin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9012-30-0 HCAPLUS
CN Acetyltransferase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9013-05-2 HCAPLUS
CN Phosphatase (9CI) (CA INDEX NAME)

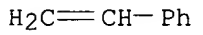
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9032-92-2 HCAPLUS
CN Glycosidase (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT **409-21-2**, Silicon carbide, uses **9003-53-6**, Polystyrene
9011-14-7, Polymethylmethacrylate **31900-57-9**,
Polydimethylsiloxane
RL: DEV (Device component use); USES (Uses)
(high d. protein arrays for screening of protein activity)
RN 409-21-2 HCAPLUS
CN Silicon carbide (SiC) (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 9003-53-6 HCAPLUS
CN Benzene, ethenyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

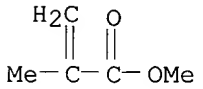
CRN 100-42-5
CMF C8 H8



RN 9011-14-7 HCAPLUS
CN 2-Propenoic acid, 2-methyl-, methyl ester, homopolymer (9CI) (CA INDEX NAME)

CM 1

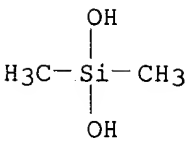
CRN 80-62-6
CMF C5 H8 O2



RN 31900-57-9 HCAPLUS
CN Silanediol, dimethyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 1066-42-8
CMF C2 H8 O2 Si



IT **372092-80-3**, Protein kinase
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(protein kinase; high d. protein arrays for screening of protein activity)
RN 372092-80-3 HCAPLUS
CN Kinase (phosphorylating), protein (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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=> d ind 1 .

L8   ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2002 ACS
IC   ICM  C12Q001-68
CC   9-1 (Biochemical Methods)
     Section cross-reference(s): 7, 38
ST   protein chip activity polymer enzyme immobilization
     genome
IT   Proteins, specific or class
     RL: ARG (Analytical reagent use); DEV (Device component use); ANST
     (Analytical study); USES (Uses)
        (DNA-binding; high d. protein arrays for screening of protein activity)
IT   Animal tissue
        (autologous; high d. protein arrays for screening of protein activity)
IT   Biotechnology
        (biochips; high d. protein arrays for screening of protein activity)
IT   Antibodies
     RL: ARG (Analytical reagent use); DEV (Device component use); ANST
     (Analytical study); USES (Uses)
        (chimeric; high d. protein arrays for screening of protein activity)
IT   Antigens
     RL: ARG (Analytical reagent use); DEV (Device component use); ANST
     (Analytical study); USES (Uses)
        (disease-specific; high d. protein arrays for screening of protein
        activity)
IT   Immobilization, biochemical
        (enzyme; high d. protein arrays for screening of protein activity)
IT   Immunoglobulins
     RL: ARG (Analytical reagent use); DEV (Device component use); ANST
     (Analytical study); USES (Uses)
        (fragments, Fab; high d. protein arrays for screening of protein
        activity)
IT   Antiserums
     Atomic force microscopy
     Bacteria (Eubacteria)
     Cell
     Ceramics
     Crosslinking agents
     Drug screening
     Fluorescent substances
     Fluorometry
     Genome
     Immobilization, biochemical
     Insect (Insecta)
     Luminescence, chemiluminescence
     Lymphocyte
     Mammal (Mammalia)
     Mass spectrometry
     Mitogens
     Molds (forms)
     Pathogen
     Protein motifs
     Radiochemical analysis
     Test kits
     Yeast
        (high d. protein arrays for screening of protein activity)
IT   Proteins, general, analysis
     RL: ANT (Analyte); PRP (Properties); ANST (Analytical study)
        (high d. protein arrays for screening of protein activity)
```

IT Antigens
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); DEV (Device component use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(high d. protein arrays for screening of protein activity)
IT Antibodies
RL: ARG (Analytical reagent use); BPN (Biosynthetic preparation); DEV (Device component use); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(high d. protein arrays for screening of protein activity)
IT DNA
Enzymes, uses
Immunoglobulins
Phospholipids, uses
Probes (nucleic acid)
RNA
Receptors
Steroids, uses
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)
IT Polyimides, uses
Polymers, uses
Silicone rubber, uses
RL: DEV (Device component use); USES (Uses)
(high d. protein arrays for screening of protein activity)
IT Reagents
RL: NUU (Other use, unclassified); USES (Uses)
(high d. protein arrays for screening of protein activity)
IT Proteins, specific or class
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(hormone binding; high d. protein arrays for screening of protein activity)
IT Antibodies
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(humanized; high d. protein arrays for screening of protein activity)
IT Immunoassay
(immunoblotting; high d. protein arrays for screening of protein activity)
IT Antibodies
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(monoclonal; high d. protein arrays for screening of protein activity)
IT Proteins, specific or class
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(nucleic acid-binding; high d. protein arrays for screening of protein activity)
IT Cellular materials
(protein-contg.; high d. protein arrays for screening of protein activity)
IT Antibodies
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(secondary, fluorescently labeled; high d. protein arrays for screening of protein activity)
IT Antibodies

RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(single chain; high d. protein arrays for screening of protein activity)

IT Glass, uses
RL: DEV (Device component use); USES (Uses)
(slide; high d. protein arrays for screening of protein activity)

IT Microscopes
(slides, glass; high d. protein arrays for screening of protein activity)

IT Antigens
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(synthetic; high d. protein arrays for screening of protein activity)

IT Antigens
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(tissue-specific; high d. protein arrays for screening of protein activity)

IT **2530-83-8**, 3-Glycidoxypropyltrimethoxysilane
RL: NUU (Other use, unclassified); USES (Uses)
(as a linker; high d. protein arrays for screening of protein activity)

IT **16833-27-5**, Oxide
RL: DEV (Device component use); USES (Uses)
(castable; high d. protein arrays for screening of protein activity)

IT **14392-02-0**, Chromium-51, analysis
RL: ANT (Analyte); ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)

IT **50-88-4**, 3H-Thymidine, uses
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)

IT **58-85-5**, Biotin **69-79-4**, Maltose **70-18-8**, Glutathione, uses **7440-02-0**, Nickel, uses **9001-92-7**, Protease **9002-07-7D**, Trypsin, derivs. **9012-30-0**, Acetylase **9013-05-2**, Phosphatase **9032-92-2**, Glycosidase
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(high d. protein arrays for screening of protein activity)

IT **409-21-2**, Silicon carbide, uses **9003-53-6**, Polystyrene **9011-14-7**, Polymethylmethacrylate **31900-57-9**, Polydimethylsiloxane
RL: DEV (Device component use); USES (Uses)
(high d. protein arrays for screening of protein activity)

IT **372092-80-3**, Protein kinase
RL: ARG (Analytical reagent use); DEV (Device component use); ANST (Analytical study); USES (Uses)
(protein kinase; high d. protein arrays for screening of protein activity)

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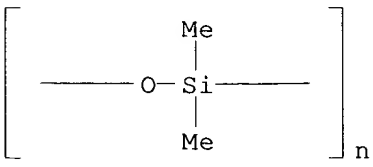
L8 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:801226 HCAPLUS
DOCUMENT NUMBER: 134:97009
TITLE: Analysis of yeast protein kinases using **protein chips**
AUTHOR(S): **Zhu, Heng; Klemic, James F.**; Chang, Swan; Bertone, Paul; Casamayor, Antonio; Klemic, Kathryn G.; Smith, David; Gerstein, Mark; **Reed, Mark A.; Snyder, Michael**
CORPORATE SOURCE: Department of Molecular, Cellular, Yale University, New Haven, CT, USA
SOURCE: Nature Genetics (2000), 26(3), 283-289
CODEN: NGENEC; ISSN: 1061-4036
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We have developed a novel **protein chip** technol. that allows the high-throughput anal. of biochem. activities, and used this approach to analyze nearly all of the protein kinases from Saccharomyces cerevisiae. **Protein chips** are disposable arrays of microwells in silicone elastomer sheets placed on top of microscope slides. The high d. and small size of the wells allows for high-throughput batch processing and simultaneous anal. of many individual samples. Only small amts. of protein are required. Of 122 known and predicted yeast protein kinases, 119 were overexpressed and analyzed using 17 different substrates and **protein chips**. We found many novel activities and that a large no. of protein kinases are capable of phosphorylating tyrosine. The tyrosine phosphorylating enzymes often share common amino acid residues that lie near the catalytic region. Thus, our study identified a no. of novel features of protein kinases and demonstrates that **protein chip** technol. is useful for high-throughput screening of protein biochem. activity.

IT **9026-43-1**, Protein kinase
RL: ANT (Analyte); ANST (Analytical study)
(anal. of yeast protein kinases using **protein chips**)
RN 9026-43-1 HCAPLUS
CN Kinase (phosphorylating), protein serine/threonine (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

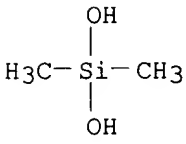
IT **9016-00-6**, PDMS **31900-57-9**, PDMS
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(anal. of yeast protein kinases using **protein chips**)
RN 9016-00-6 HCAPLUS
CN Poly[oxy(dimethylsilylene)] (8CI, 9CI) (CA INDEX NAME)



RN 31900-57-9 HCAPLUS
CN Silanediol, dimethyl-, homopolymer (9CI) (CA INDEX NAME)

CM 1

CRN 1066-42-8
CMF C2 H8 O2 Si



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ind 2

L8 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2002 ACS
CC 7-1 (Enzymes)
ST yeast protein kinase detection chip technol
IT Saccharomyces cerevisiae
(anal. of yeast protein kinases using **protein chips**
)
IT Polysiloxanes, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(anal. of yeast protein kinases using **protein chips**
)
IT Evolution
(mol.; anal. of yeast protein kinases using **protein chips**)
IT **9026-43-1**, Protein kinase
RL: ANT (Analyte); ANST (Analytical study)
(anal. of yeast protein kinases using **protein chips**
)
IT **9016-00-6**, PDMS **31900-57-9**, PDMS
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(anal. of yeast protein kinases using **protein chips**
)

=> d ibib abs hitstr 1

L17 ANSWER 1 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:152727 HCAPLUS
DOCUMENT NUMBER: 134:190331
TITLE: Multipurpose diagnostic systems using **protein chips**
INVENTOR(S): Kim, Sun-young; Yoon, Keejung; Park, Eun-jin
PATENT ASSIGNEE(S): Diachip Limited, S. Korea
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001014425	A1	20010301	WO 2000-KR928	20000819

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: KR 1999-34427 A 19990819

AB The present invention provides **protein chips** on which high d. of protein probe arrays are fixed, a method for manufg. the **protein chips**, atomized diagnostic systems comprising the **protein chips** and the use thereof. The highly integrated structure of the **protein chip** makes a biochem. or an immunol. assay faster, suitable for automation, precise and easy to handle. The usage of the **protein chip** encompasses clin. diagnosis, researches for the kinetics of enzymic reactions and screening antagonists or ligands which bind to the interested receptors. In particular, the **protein chip** enables multipurpose diagnosis of various diseases for a no. of patients even by a test. Recombinant antigens from hepatitis C virus or from HIV-1 were immobilized on glass slides coated with aminoalkylsilane to make **protein chips** which were used to detect antibodies in blood serum samples. FITC-conjugated anti-human IgG and high-speed fluorescence scanning were used in the detection.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L17 ANSWER 2 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:373474 HCAPLUS
DOCUMENT NUMBER: 133:102267
TITLE: Chip is an essential cofactor for Apterous in the regulation of axon guidance in Drosophila
AUTHOR(S): Van Meyel, Donald J.; O'Keefe, David D.; Thor, Stefan; Jurata, Linda W.; Gill, Gordon N.; Thomas, John B.
CORPORATE SOURCE: The Salk Institute for Biological Studies, San Diego, CA, 92186, USA
SOURCE: Development (Cambridge, United Kingdom) (2000), 127(9), 1823-1831
CODEN: DEVPED; ISSN: 0950-1991
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LIM-homeodomain transcription factors are expressed in subsets of neurons and are required for correct axon guidance and neurotransmitter identity. The LIM-homeodomain family member Apterous requires the LIM-binding **protein Chip** to execute patterned outgrowth of the Drosophila wing. To det. whether Chip is a general cofactor for diverse LIM-homeodomain functions in vivo, the authors studied its role in the embryonic nervous system. Loss-of-function Chip mutations cause defects in neurotransmitter (FMRFamide) prodn. that mimic apterous and islet mutants. Chip is also required cell-autonomously by Apterous-expressing neurons for proper axon guidance, and requires both a homodimerization domain and a LIM interaction domain to function appropriately. Using a Chip/Apterous **chimeric** mol. lacking domains normally required for their interaction, the authors reconstituted the complex and rescued the axon guidance defects of apterous mutants, of Chip mutants and of embryos doubly mutant for both apterous and Chip. The authors' results indicate that Chip participates in a range of developmental programs controlled by LIM-homeodomain proteins and that a tetrameric complex comprising two Apterous mols. bridged by a Chip homodimer is the functional unit through which Apterous acts during neuronal differentiation.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 3

L17 ANSWER 3 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:602016 HCAPLUS
DOCUMENT NUMBER: 131:297769
TITLE: Chip and apterous physically interact to form a functional complex during Drosophila development
AUTHOR(S): Van Meyel, Donald J.; O'Keefe, David D.; Jurata, Linda W.; Thor, Stefan; Gill, Gordon N.; Thomas, John B.
CORPORATE SOURCE: The Salk Institute for Biological Studies, La Jolla, CA, 92037, USA
SOURCE: Mol. Cell (1999), 4(2), 259-265
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB LIM homeodomain (LIM-HD) proteins play key roles in a variety of developmental processes throughout the animal kingdom. Here we show that the LIM-binding **protein Chip** acts as a cofactor for the Drosophila LIM-HD family member Apterous (Ap) in wing development. We define the domains of Chip required for LIM-HD binding and for homodimerization and show that mutant proteins deleted for these domains act in a dominant-neg. fashion to disrupt Ap function. Our results support a model for multimeric complexes contg. Chip and Ap in transcriptional regulation. This model is confirmed by the activity of a **chimeric** fusion between Chip and Ap that reconstitutes the complex and rescues the ap mutant phenotype.
REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 4

L17 ANSWER 4 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:507437 HCAPLUS
DOCUMENT NUMBER: 122:284995
TITLE: Water channel properties of major intrinsic protein of lens
AUTHOR(S): Mulders, Sabine M.; Preston, Gregory M.; Deen, Peter M. T.; Guggino, William B.; van Os, Carel H.; Agre, Peter
CORPORATE SOURCE: Dep. Cell Physiol., Univ. Nijmegen, Nijmegen, 6500 HB, Neth.
SOURCE: J. Biol. Chem. (1995), 270(15), 9010-16
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The functions of major intrinsic protein (MIP) of lens are still unresolved; however the sequence homol. with channel-forming integral membrane **protein** (**CHIP**) and other Aquaporins suggests that MIP is a water channel. Immunolocalizations confirmed that Xenopus oocytes injected with bovine MIP cRNA express the protein and target it to the plasma membrane. Control oocytes or oocytes expressing MIP or CHIP exhibited small, equiv. membrane currents that could be reversibly increased by osmotic swelling. When compared with water-injected control oocytes, the coeff. of osmotic water permeability (Pf) of MIP oocytes was increased 4-5-fold with a low Arrhenius activation energy, while the Pf of CHIP oocytes increased >30-fold. To identify structures responsible for these differences in Pf, recombinant MIP proteins were expressed. Anal. of MIP-CHIP **chimeric** proteins revealed that the 4-kDa cytoplasmic domain of MIP did not behave as a neg. regulator. Individual residues in MIP were replaced by residues conserved among the Aquaporins, and introduction of a proline in the 5th transmembrane domain of MIP raised the Pf by 50%. Thus oocytes expressing MIP failed to exhibit ion channel activity and consistently exhibited water transport by a facilitated pathway that was qual. similar to the Aquaporins but of lesser magnitude. The authors conclude that MIP functions as an Aquaporin in lens, but the protein may also have other essential functions.

=> d ibib abs hitstr 5

L17 ANSWER 5 OF 5 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1984:543746 HCAPLUS
DOCUMENT NUMBER: 101:143746
TITLE: Differential effect of cyclosporin A on the expression of T and B **lymphocyte activation** antigens
AUTHOR(S): Lillehoj, Hyun S.; Malek, Thomas R.; Shevach, Ethan M.
CORPORATE SOURCE: Lab. Immunol., Natl. Inst. Allergy Infect. Dis., Bethesda, MD, 20205, USA
SOURCE: J. Immunol. (1984), 133(1), 244-50
CODEN: JOIMA3; ISSN: 0022-1767
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A monoclonal antibody (Mab) to the interleukin 2 (IL 2) receptor as well as a Mab to the transferrin receptor was used to analyze the effects of cyclosporin A (CsA) [59865-13-3] on the induction and expression of these activation antigens on **mitogen**-stimulated murine T and B lymphocytes. The same concn. (0.25 .mu.g/mL) of CsA that produced optimal inhibition of the T cell proliferative response to concanavalin A (Con A) was also very effective at inhibiting IL 2 prodn. and the induction of IL 2 responsiveness, as well as the expression of the IL 2 and transferrin receptors when measured 72 h after **mitogen** activation. Surprisingly, CsA only minimally inhibited expression of these receptors 24 h after the addn. of **mitogen**; however, T cell blasts recovered from these cultures failed to respond to IL 2 even though IL 2 receptor expression was only modestly decreased. Apparently inhibition of the maturation of receptor expression is **secondary** to an early effect of CsA in blocking the induction of IL 2 responsiveness or to an arrest in the sequence of events required for maturation of T **cells** that bear **high densities** of these receptors. In contrast to the results obsd. with T lymphocytes, CsA had no effect on the B cell proliferative response to lipopolysaccharide or on the induction of the IL 2 and transferrin receptors on **activated** B **lymphocytes**.

=> d ibib abs hitstr 1

L22 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:904740 HCAPLUS
DOCUMENT NUMBER: 136:17685
TITLE: Screening of phage displayed peptides without clearing of the cell culture
INVENTOR(S): Nock, Steffen; Kassner, Paul D.
PATENT ASSIGNEE(S): Zyomyx, Inc., USA
SOURCE: PCT Int. Appl., 39 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001094950	A2	20011213	WO 2001-US18421	20010605

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-209503P P 20000605
US 2001-874547 A 20010604

AB The invention concerns methods for screening populations of phage-displayed **polypeptides** that are particularly **well**-suited for **high**-throughput screening. The methods do not require the clearing of cells from a culture used to obtain the population of phage or other replicable genetic packages. Accordingly, the invention provides methods for forming complexes between a replicable genetic package displaying a polypeptide fusion and a target mol. in an uncleared cell culture contg. replicable genetic package. Compns. made up of an uncleared cell culture contg. replicable genetic packages displaying a polypeptide fusion and a target mol. are provided in the invention as well.

=> d ibib abs hitstr 2

L22 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:816983 HCAPLUS
DOCUMENT NUMBER: 135:354956
TITLE: **High density protein arrays** for screening of **protein** activity
INVENTOR(S): Snyder, Michael; Reed, Mark; Zhu, Heng; Klemic, James Frank
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 69 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001083827	A1	20011108	WO 2001-US14526	20010504

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-201921P P 20000504
US 2000-221034P P 20000727

AB The invention concerns protein chips useful for the large-scale study of protein function where the chip contains densely packed reaction wells. The invention also relates to methods of using protein chips to assay simultaneously the presence, amt., and/or function of proteins present in a protein sample or on one protein chip, or to assay the presence, relative specificity, and binding affinity of each probe in a mixt. of probes for each of the proteins on the chip. The invention also relates to methods of using the protein chips for high d. and small vol. chem. reactions. Also, the invention relates to **polymers** useful as protein chip substrates and methods of making protein chips. The invention further relates to compds. useful for the derivatization of protein chip substrates.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 3

L22 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:608802 HCAPLUS
DOCUMENT NUMBER: 132:191317
TITLE: A homogenous 384-well high throughput screen for novel tumor necrosis factor receptor: ligand interactions using time resolved energy transfer
AUTHOR(S): Moore, K. J.; Turconi, S.; Miles-Williams, A.; Djaballah, H.; Hurskainen, P.; Harrop, J.; Murray, K. J.; Pope, A. J.
CORPORATE SOURCE: Department of Molecular Screening Technologies, SmithKline Beecham Pharmaceuticals, Essex, UK
SOURCE: J. Biomol. Screening (1999), 4(4), 205-214
CODEN: JBISF3; ISSN: 1087-0571
PUBLISHER: Mary Ann Liebert, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The herpes virus entry mediator (HVEM) receptor and its ligand, HVEM-L, are involved in both herpes simplex virus type-1 (HSV-1) herpes simplex virus type-2 (HSV-2) infection, and in T-cell activation such that antagonists of this interaction are expected to have utility in viral and inflammatory diseases. In this report we describe the configuration of a homogeneous 384-well assay based on time-resolved energy transfer from a europium chelate on the HVEM receptor to an allophycocyanin (APC) acceptor on the ligand. Specific time resolved emission from the acceptor is obsd. on receptor:ligand complex formation. The results of various direct and indirect labeling strategies are described. Several assay optimization expts. were necessary to obtain an assay that was robust to automation and file compd. interference while sensitive to the effect of potential inhibitors. The signal was stable for more than 24 h at room temp. using the Eu3+ chelates, suggesting no dissocn. of the lanthanide ion. The 384-well assay was readily automated and was able to identify more than 99.5% of known pos. controls in the validation studies successfully. Screening identified both a series of known potent inhibitors and several structural classes of hits that readily deconvoluted to yield single compd. inhibitors with the desired functional activity in **secondary** biol. assays. The equivalence of the data in 384- and 1536-well formats indicates that routine implementation of 1536-well chelate-based energy transfer screening appears to be primarily limited by liq. handling rather than detection issues.
REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic 3

L22 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
AB . . . and several structural classes of hits that readily deconvoluted to yield single compd. inhibitors with the desired functional activity in **secondary** biol. assays. The equivalence of the data in 384- and 1536-well formats indicates that routine implementation of 1536-well chelate-based energy. . .
IT **Cell** activation
(T **cell**; homogeneous 384-**well high** throughput screen for novel tumor necrosis factor receptor - ligand interactions using time resolved energy transfer)
IT T **cell** (**lymphocyte**)
(**activation**; homogeneous 384-**well high** throughput screen for novel tumor necrosis factor receptor - ligand interactions using time resolved energy transfer)

=> d ibib abs hitstr 4

L22 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:535032 HCAPLUS
DOCUMENT NUMBER: 125:212955
TITLE: Discriminative analysis of rat Sertoli and peritubular cells and their proliferation in vitro: evidence for follicle-stimulating hormone-mediated contact inhibition of Sertoli cell mitosis
AUTHOR(S): Schlatt, Stefan; de Kretser, David M.; Loveland, Kate L.
CORPORATE SOURCE: Inst. Reproduction Development, Monash Univ., Clayton, Australia
SOURCE: Biol. Reprod. (1996), 55(2), 227-235
CODEN: BIREBV; ISSN: 0006-3363
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new methodol. approach using immunohistochem. markers for Sertoli cells (alpha inhibin), peritubular cells (alpha smooth muscle actin), and S-phase cells (bromodeoxyuridine; BrdU) is presented that allows an accurate and simultaneous anal. of morphogenetic and **mitogenic** changes occurring in vitro. Sertoli cells and peritubular cells were isolated by sequential enzymic digestion from 7-day-old rats. Laminin, as a major component of the extracellular matrix of the seminiferous tubule, and FSH, as a hormone stimulating Sertoli cell proliferation, were tested for their ability to influence the morphol. or mitotic activity of the cultured cells. After fixation, the coverslips were stained for these antigens with use of specific primary antibodies and horseradish peroxidase- or alk. phosphatase-labeled **secondary** antibodies for visualization of the resp. antigens with different-colored ppts. This approach allowed us to distinguish the two cell populations, which could not be done unequivocally without the antibody staining. We scored striking changes in cell densities and cell ratios during the culture period. Peritubular cells showed a consistently higher BrdU-labeling index than Sertoli cells. While Sertoli cells were not labeled until Day 7, peritubular cells proliferated as soon as on Day 3, and their d. doubled from Day 3 to Day 7. A linear neg. correlation was established for Sertoli cell proliferation in response to their local d. on the coverslip, indicating contact inhibition as a signal for cessation of mitosis. At **high cell densities**, this inhibition was partially overcome in the presence of FSH. The presence of laminin had striking effects on the morphogenetic response but only a minor influence on **mitogenesis**.

=> d ibib abs hitstr 1

L32 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:85890 HCAPLUS
TITLE: Generating addressable protein microarrays with PROfusion covalent mRNA-protein fusion technology
AUTHOR(S): Weng, Shawn; Gu, Ke; Hammond, Philip W.; Lohse, Peter; Rise, Cecil; Wagner, Richard W.; Wright, Martin C.; Kuimelis, Robert G.
CORPORATE SOURCE: Phylos, Lexington, MA, 02421, USA
SOURCE: Proteomics (2002), 2(1), 48-57
CODEN: PROTC7; ISSN: 1615-9853
PUBLISHER: Wiley-VCH Verlag GmbH
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An mRNA-protein fusion consists of a polypeptide covalently linked to its corresponding mRNA. These species, prepd. individually or en masse by in vitro translation with a modified mRNA conjugate (the PROfusion process), link phenotype to genotype and enable powerful directed evolution schemes. We have exploited the informational content of the nucleic acid component of the mRNA-protein fusion to create an addressable protein microarray that self-assembles via hybridization to surface-bound DNA capture probes. The nucleic acid component not only directs the mRNA-protein fusion to the proper coordinate of the microarray, but also **positions** the protein in a uniform orientation. We demonstrate the feasibility of this **protein chip** concept with several mRNA-protein fusions, each possessing a unique peptide epitope sequence. These addressable proteins could be visualized on the microarray both by autoradiog. and highly specific monoclonal antibody binding. The anchoring of the protein to the chip surface is surprisingly robust, and the system is sensitive enough to detect sub-attomole quantities of displayed protein without signal amplification. Such protein **arrays** should be useful for functional screening in massively parallel formats, as well as other applications involving immobilized peptides and proteins.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L32 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:335116 HCAPLUS
DOCUMENT NUMBER: 122:234775
TITLE: Oligonucleotide-directed self-assembly of proteins: semisynthetic DNA-streptavidin hybrid molecules as connectors for the generation of macroscopic **arrays** and the construction of supramolecular bioconjugates
AUTHOR(S): Niemeyer, Christof M.; Sano, Takeshi; Smith, Cassandra L.; Cantor, Charles R.
CORPORATE SOURCE: Cent. Adv. Biotechnol., Boston Univ., Boston, MA, 02215, USA
SOURCE: Nucleic Acids Res. (1994), 22(25), 5530-9
CODEN: NARHAD; ISSN: 0305-1048
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Modified biomols. were used for the non-covalent assembly of novel bioconjugates. Hybrid mols. were synthesized from short single-stranded DNA and streptavidin by chem. methods using a heterobispecific crosslinker. The covalent attachment of an oligonucleotide moiety to streptavidin provides a specific recognition domain for a complementary nucleic acid sequence, in addn. to the four native biotin-binding sites. These bispecific binding capabilities allow the hybrid mols. to serve as versatile connectors in a variety of applications. Bifunctional constructs have been prepd. from two complementary hybrid mols., each previously conjugated to biotinylated IgG or alk. phosphatase. The use of nucleic acid or proteins is further demonstrated on two size scales. A macroscopic DNA **array** on a microtiter plate has been transformed into a comparable **protein chip**. A nano-scale **array** was made by hybridizing DNA-tagged proteins to specific **positions** along a RNA or DNA sequence. The generation of supramol. bioconjugates were shown by quant. measurements and gel-retardation assays.

=> d ibib abs hitstr 3

L32 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:550146 HCAPLUS
DOCUMENT NUMBER: 119:150146
TITLE: Conformal chemical beam **deposition** of thin metal film for fabricating **high density** trench capacitor **cells**
AUTHOR(S): Hsu, David S. Y.; Gray, Henry F.
CORPORATE SOURCE: Chem. Div., Nav. Res. Lab., Washington, DC, 20375-5320, USA
SOURCE: Appl. Phys. Lett. (1993), 63(2), 159-61
CODEN: APPLAB; ISSN: 0003-6951
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The difficult aspect of conformal metal film **deposition** in narrow, high aspect ratio trenches such as those used in the fabrication of high-d. MOS trench capacitor cells for computer memory technol. is addressed. This work demonstrates the proof of principle of highly conformal **deposition** of a 40-nm Pt film on the surfaces of a 0.5-.mu.m-wide, 1.5-.mu.m-deep, and 2-mm-long **array** of oxidized **silicon** trenches, using the thermal decompn. of a mol. precursor under chem. beam conditions. In addn., scanning electron, x-ray photoelectron, and scanning Auger electron **microscopy** analyses reveal highly uniform and complete coverage on all surfaces, small metal grain size, and the absence of detectable impurities.

=> d ibib abs hitstr 4

L32 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1983:467081 HCAPLUS
DOCUMENT NUMBER: 99:67081
TITLE: Use of in situ hybridization to identify collagen and albumin mRNAs in isolated mouse hepatocytes
AUTHOR(S): Saber, Mohamed A.; Zern, Mark A.; Shafritz, David A.
CORPORATE SOURCE: Liver Res. Cent., Albert Einstein Coll. Med., Bronx, NY, 10461, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1983), 80(13), 4017-20
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The title cells were isolated by collagenase perfusion, mincing, and differential centrifugation. Nick-translated 3H-labeled mouse albumin cDNA (pmalb-2) and chicken pro-.alpha.2(I) collagen cDNA (pCg45) probes were then hybridized with the cells in **silane**-treated microcentrifuge tubes. The cells were transferred and fixed to a **microscope slide**, and hybridization was evaluated semiquant. by counting exposure of grains in autoradiog. emulsion placed over the cells. With this method of in-situ hybridization, all hepatocytes appear to have significant, but highly variable, amts. of albumin mRNA. In addn., type-I procollagen mRNA appears to be present at low abundance in hepatocytes. These results indicate that in-situ hybridization can effectively demonstrate the presence of specific low- or **high**-abundance mRNAs in isolated **well**-differentiated eukaryotic **cells**.

=> d ibib abs hitstr 1

L38 ANSWER 1 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:808079 HCAPLUS
DOCUMENT NUMBER: 132:134319
TITLE: Profiling of amyloid .beta. peptide variants using SELDI **protein chip arrays**
AUTHOR(S): Davies, Huw; Lomas, Lee; Austen, Brian
CORPORATE SOURCE: Ciphergen Biosystems, Surry, UK
SOURCE: BioTechniques (**1999**), 27(6), 1258-1261
CODEN: BTNQDO; ISSN: 0736-6205
PUBLISHER: Eaton Publishing Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The profile of amyloid .beta. (A.beta.) peptide variants secreted into the media of human cultured cells that express the amyloid precursor protein was examd. by Surface Enhanced Laser Desorption/Ionization (SELDI) ProteinChip technol. from Ciphergen Biosystems using biol. active ProteinChip **Arrays**. An anti-A.beta. polyclonal antibody (anti-NTA4) was used to capture and purify multiple immunoreactive A.beta. fragments from a single microliter of media onto the ProteinChip **Array**. Fragments retained on the surface of the ProteinChip **Array** were detected directly by mass in the ProteinChip System to provide detailed information on the identity of different A.beta. variants secreted from the cultured cells. We discuss existing and potential applications of this immunoassay for the detection and relative quantitation of A.beta. species from both cultured cell systems and clin. samples.
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 2

L38 ANSWER 2 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:144013 HCAPLUS
TITLE: **Protein chip array** strategies for differential protein display: Retentate maps of molecular recognition diversity
AUTHOR(S): Weinberger, Scot R.; Yip, Tai-Tung; Thatcher, Bradley J.; Pham, Thang T.; Hutchens, T. William
CORPORATE SOURCE: Ciphergen Biosystems Inc., Palo Alto, CA, 94306, USA
SOURCE: Book of Abstracts, 217th ACS National Meeting, Anaheim, Calif., March 21-25 (**1999**), ANYL-179. American Chemical Society: Washington, D. C.
CODEN: 67GHA6
DOCUMENT TYPE: Conference; Meeting Abstract
LANGUAGE: English
AB Since the advent of the Human Geonome Project, we have witnessed. > unparalleled growth in the demand for characterizing biol. > expression within living systems. Differential biol. and cellular. > diversity is being explored on both genotypic and phenotypic levels. > While the recent past has witnessed significant advances in DNA and. > RNA anal. such as on-chip hybridization; high thruput, microscale,. > Sanger-like sequencing approaches; and denaturing chromatog. > techniques, advances in the anal. of proteins have primarily.

=> d ibib abs hitstr 3

L38 ANSWER 3 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:85856 HCAPLUS
DOCUMENT NUMBER: 130:240924
TITLE: New type of Sintered SiC fiber and its composite material
AUTHOR(S): Ishikawa, Toshihiro; Kajii, Shinji; Hisayuki, Terumi; Kohtoku, Yasuhiko
CORPORATE SOURCE: Ube Research Laboratories, Ube Industries Ltd., Ube City, 755, Japan
SOURCE: Ceram. Eng. Sci. Proc. (**1998**), 19(3), 283-290
CODEN: CESPDK; ISSN: 0196-6219
PUBLISHER: American Ceramic Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB This paper deals with a new type of sintered SiC fiber with excellent heat-resistance and mech. properties, and a unique composite material composed of only the sintered SiC fiber. We report here that the sintered SiC fiber contg. a very small amt. of Al showed high-strength, high-modulus, excellent high temp. stability and prominent alkali-resistance. Moreover, the fiber showed **excellent** creep resistance at very **high** temps. compared with **well** -known SiC-based fibers. This sintered SiC fiber was synthesized at a very high temp. (over 2073K) using an amorphous Si-Al-C-O fiber as the starting material. Its high strength over 2 GPa was maintained up to 2273K in Ar atm. and very little wt. loss (only 1.8wt%) was obsd. up to 2473K. On the basis of this technol., we have also succeeded in developing a toughened fiber-bonded composite, consisting of perfectly close-packed sintered SiC fibers with a hexagonal transformed cross-section. At the interface between the hexagonal-columnar fibers a very thin interfacial carbon layer uniformly exists to obtain fibrous fracture pattern. The sintered fiber-bonded composite, having very high fiber vol. fraction (.apprx. 100%), showed excellent oxidn. resistance up to 1873K in air and perfectly maintained the initial high strength even at that high temps.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 4

L38 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:450325 HCAPLUS
DOCUMENT NUMBER: 125:137084
TITLE: Cryo-electron **microscopy** of **polymer** particles in a **high cell density** synthetic biofilm
AUTHOR(S): Thiagarajan, V.; Ming, Y.; Scriven, L. E.; Flickinger, M. C.
CORPORATE SOURCE: Biological Process Technology Institute, University Minnesota, Saint Paul, MN, 55108-6106, USA
SOURCE: Prog. Biotechnol. (**1996**), 11(Immobilized Cells), 298-303
CODEN: PBITE3; ISSN: 0921-0423
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cryogenic SEM appears to be a useful method to visualize the **polymer** particles and cells in acrylic/vinyl acetate synthetic biofilms without the loss of cell structure which would normally occur in SEM samples prepd. by dehydration. E. coli strain ZK211 did not appear to be significantly reduced in size or altered in shape following entrapment in copolymer, drying, and rehydration, when compared to the shape and size obsd. in suspension culture. This corroborates the cell viability data indicating that following immobilization and film rehydration, the viability of E. coli cells is not significantly reduced from that of suspended cells from which the film was prepd. This method also appears useful to evaluate the av. **polymer** particle size, particle size distribution, the interface between film layers, hydrated film thickness, and particle coalescence for different **polymers** as a function of drying/curing and rehydration conditions.

=> d kwic 4

L38 ANSWER 4 OF 7 HCAPLUS COPYRIGHT 2002 ACS
TI Cryo-electron **microscopy** of **polymer** particles in a **high cell density** synthetic biofilm
SO Prog. Biotechnol. (**1996**), 11(Immobilized Cells), 298-303
CODEN: PBITE3; ISSN: 0921-0423
AB Cryogenic SEM appears to be a useful method to visualize the **polymer** particles and cells in acrylic/vinyl acetate synthetic biofilms without the loss of cell structure which would normally occur in SEM. . . from that of suspended cells from which the film was prepd. This method also appears useful to evaluate the av. **polymer** particle size, particle size distribution, the interface between film layers, hydrated film thickness, and particle coalescence for different **polymers** as a function of drying/curing and rehydration conditions.
ST cryogenic SEM biofilm **polymer** particle
IT Biofilms (microbial reactor)
Escherichia coli
(cryoelectron **microscopy** of **polymer** particles in a high cell d. synthetic biofilm)
IT **Polymers**, biological studies
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(particles; cryoelectron **microscopy** of **polymer** particles in a high cell d. synthetic biofilm)

IT **Microscopy**, electron
(scanning, cryo-; cryoelectron **microscopy** of **polymer** particles in a high cell d. synthetic biofilm)

IT 24980-58-3, Acrylic acid-vinyl acetate copolymer
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(cryoelectron **microscopy** of **polymer** particles in a high cell d. synthetic biofilm)

=> d ibib abs hitstr 5

L38 ANSWER 5 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1991:681242 HCAPLUS
DOCUMENT NUMBER: 115:281242
TITLE: Reinforcing **high-density** polyethylene with **cellulosic** fibers. I. The effect of additives on fiber dispersion and mechanical properties
AUTHOR(S): Raj, R. G.; Kokta, B. V.
CORPORATE SOURCE: Cent. Rech. Pates Pap., Univ. Quebec, Trois-Rivieres, PQ, G9A 5H7, Can.
SOURCE: Polym. Eng. Sci. (**1991**), 31(18), 1358-62
CODEN: PYESAZ; ISSN: 0032-3888
DOCUMENT TYPE: Journal
LANGUAGE: English
AB HDPE was reinforced with 0-40% of wood flour (aspen). The effects of stearic acid (I), mineral oil, maleated polyethylene wax, and Na silicate on the tensile and impact strength of the composite were studied. The comparison of tensile properties of the composites showed that the addn. of the wax produced a significant increase in tensile strength, with the increase in filler concn., while the tensile modulus remained relatively unaffected. **Microscopic** studies of the composites indicated a better dispersion of the fibers in the **polymer** matrix when I was used.

=> d ibib abs hitstr 6

L38 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:631826 HCAPLUS
DOCUMENT NUMBER: 105:231826
TITLE: Structure and dynamics of anaerobic bacterial aggregates in a gas-lift reactor
AUTHOR(S): Beeftink, H. H.; Staugaard, P.
CORPORATE SOURCE: Dep. Chem. Technol., Univ. Amsterdam, Amsterdam, 1018 WV, Neth.
SOURCE: Appl. Environ. Microbiol. (**1986**), 52(5), 1139-46
CODEN: AEMIDF; ISSN: 0099-2240
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Anaerobic mixed-culture aggregates, which converted glucose [50-99-7] to AcOH [64-19-7], propionic [79-09-4], butyric [107-92-6], and valeric [109-52-4] acids, were formed under controlled conditions of substrate feed (C limitation) and hydraulic regimen. The continuous-flow system used (anaerobic gas-lift reactor) was designed to retain bacterial aggregates in a **well**-mixed reactor. Carrier availability (i.e., liq.-suspended sand grains) was necessary for bacterial aggregate formation from individual cells during reactor start-up. Electron **microscopic** examn. revealed that incipient colonization of sand grains by bacteria from the bulk liq. occurred in surface irregularities, conceivably reflecting local quiescence. Subsequent confluent biofilm formation on sand grains was unstable. Substrate depletion in the bulk liq. is assumed to weaken deeper parts of the biofilm due to cellular lysis, after which prodn. of gas bubbles and liq. shearing forces cause sloughing. The resulting fragments, although sand free, were large enough to be retained in the reactor and gradually grew larger through bacterial growth and by clumping together with other fragments. In the final steady state, **high cell densities** were maintained in the form of aggregates, while sand had virtually disappeared due to sampling losses and wash-out. Numerical cell densities within aggregates ranged from 1012 mL at the periphery to very low values in the center. The cells were enmeshed in a **polymer** matrix contg. polysaccharides; nevertheless, carbon sufficiency was not a prerequisite to sustain high hold-up ratios.

=> d ibib abs hitstr 7

L38 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1981:78765 HCAPLUS
DOCUMENT NUMBER: 94:78765
TITLE: Organization of the core lipids of high density lipoproteins in the lactating bovine
AUTHOR(S): Tall, Alan R.; Puppione, Donald L.; Kunitake, Steven T.; Atkinson, David; Small, Donald M.; Waugh, David
CORPORATE SOURCE: Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SOURCE: J. Biol. Chem. (**1981**), 256(1), 170-4
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB High-d. lipoprotein (HDL) from lactating Jersey and Holstein cows were fractionated by isopycnic d. gradient ultracentrifugation, and individual fractions between densities 1.06 and 1.13 g/mL were examd. by differential scanning calorimetry and neg. stain electron **microscopy**. With increasing d., particles decreased in mean diam. from 16.0 to 9.0 nm. Scanning calorimetry of HDL of diams. 12.0 to 16.0 nm showed a reversible thermal transition between 20 and 35.degree., resembling the liq. cryst. transitions of cholesterol esters in the lipid ext. of bovine HDL. The enthalpy of this transition was markedly reduced compared to pure cholesterol esters or to the cholesterol ester transitions described previously in larger cholesterol ester-rich lipoproteins. Scanning calorimetry of bovine HDL of diam. less than 12.0 nm showed no thermal transitions between 0 and 60.degree.. However, the disappearance of the low temp. cholesterol ester transition was assocd. with the appearance at high temps. (94-113.degree.) of a distinct 2nd component of the lipoprotein denaturation endotherm. This component represented a const. entropy change of cholesterol ester (0.0032 cal/g/.degree.) which was similar to that of the smectic-liq. transition of pure cholesterol esters. Thus, as HDL particles decrease in diam. from 16.0 to 12.0 nm, their core probably becomes too small to allow melting of liq. cryst. cholesterol esters. The high temp. component of the thermal denaturation of small HDL particles may be due to disordering of cholesterol esters that possibly becomes **secondary** to lipoprotein disruption.

=> d ibib abs hitstr 1

L39 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:28017 HCAPLUS
DOCUMENT NUMBER: 130:92457
TITLE: Retentate chromatography and **protein chip arrays** with applications in biology and medicine
INVENTOR(S): Hutchens, T. William; Yip, Tai-tung
PATENT ASSIGNEE(S): Ciphergen Biosystems, Inc., USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9859362	A1	19981230	WO 1998-US12908	19980619 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9884721	A1	19990104	AU 1998-84721	19980619 <--
EP 990258	A1	20000405	EP 1998-935479	19980619 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI				
JP 2000516727	T2	20001212	JP 1999-504918	19980619 <--
US 6225047	B1	20010501	US 1998-100302	19980619 <--
NO 9906243	A	20000217	NO 1999-6243	19991216 <--
US 2001014461	A1	20010816	US 2000-745388	20001221 <--

PRIORITY APPLN. INFO.:
US 1997-54333P P 19970620 <--
US 1997-67484P P 19971201 <--
US 1998-100302 A3 19980619 <--
WO 1998-US12908 W 19980619 <--

AB This invention provides methods of retentate chromatog. for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biol. and medicine, including clin. diagnostics and drug discovery.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic

L39 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
TI Retentate chromatography and **protein chip arrays** with applications in biology and medicine
PRAI US 1997-54333P P 19970620 <--
US 1997-67484P P 19971201 <--
US 1998-100302 A3 19980619 <--
WO 1998-US12908 W 19980619 <--
DT **Patent**

ST retentate chromatog **protein chip array**

IT Adsorbents
Animal tissue
Blood analysis
Body fluid
Cell (biological)
Chromatography
Culture media
Diagnosis
Diseases (animal)
Infant
Phage display
Serum (blood)
Time-of-flight mass spectrometry
Tumors (animal)
Urine analysis
(retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

IT Antigens
Ligands
Proteins (general), analysis
RL: ANT (Analyte); ANST (Analytical study)
(retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

IT Antibodies
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

IT Receptors
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

IT 7440-50-8, Copper, analysis
RL: ARU (Analytical role, unclassified); ANST (Analytical study)
(TED-; retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

IT 9001-63-2, Lysozyme
RL: ANT (Analyte); ANST (Analytical study)
(retentate chromatog. and **protein chip arrays** with applications in biol. and medicine)

=> d ibib abs hitstr 2

L39 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:28016 HCAPLUS
DOCUMENT NUMBER: 130:92456
TITLE: Retentate chromatography and **protein chip arrays** with applications in biology and medicine
INVENTOR(S): Hutchens, T. William; Yip, Tai-tung
PATENT ASSIGNEE(S): Ciphergen Biosystems, Inc., USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9859361	A1	19981230	WO 1998-US12907	19980619 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9883753	A1	19990104	AU 1998-83753	19980619 <--
EP 990257	A1	20000405	EP 1998-934162	19980619 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
US 6225047	B1	20010501	US 1998-100302	19980619 <--
US 2001014461	A1	20010816	US 2000-745388	20001221 <--

PRIORITY APPLN. INFO.:
US 1997-54333P P 19970620 <--
US 1997-67484P P 19971201 <--
US 1998-100302 A3 19980619 <--
WO 1998-US12907 W 19980619 <--

AB This invention provides methods of retentate chromatog. for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biol. and medicine, including clin. diagnostics and drug discovery.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 3

L39 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:28015 HCAPLUS
DOCUMENT NUMBER: 130:78445
TITLE: Retentate chromatography and **protein chip arrays** with applications in biology and medicine
INVENTOR(S): Hutchens, T. William; Yip, Tai-tung
PATENT ASSIGNEE(S): Ciphergen Biosystems, Inc., USA
SOURCE: PCT Int. Appl., 157 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9859360	A1	19981230	WO 1998-US12843	19980619 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9879816	A1	19990104	AU 1998-79816	19980619 <--
EP 990256	A1	20000405	EP 1998-930421	19980619 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI				
US 6225047	B1	20010501	US 1998-100302	19980619 <--
JP 2002507282	T2	20020305	JP 1999-504876	19980619 <--
US 2001014461	A1	20010816	US 2000-745388	20001221 <--

PRIORITY APPLN. INFO.:

US 1997-54333P	P	19970620 <--
US 1997-67484P	P	19971201 <--
US 1998-100302	A3	19980619 <--
WO 1998-US12843	W	19980619 <--

AB This invention provides methods of retentate chromatog. for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectively conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biol. and medicine, including clin. diagnostics and drug discovery.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d ibib abs hitstr 1

L42 ANSWER 1 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:753374 HCAPLUS
DOCUMENT NUMBER: 132:1780
TITLE: Method and device for photolithographic production of DNA, PNA and **protein chips**
INVENTOR(S): Heuermann, Arno Svend
PATENT ASSIGNEE(S): Epigenomics G,m,b,H., Germany
SOURCE: PCT Int. Appl., 15 pp.
CODEN: PIXXD2
DOCUMENT TYPE: **Patent**
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9960156	A2	19991125	WO 1999-DE1524	19990517	<--
WO 9960156	A3	20000217			

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

DE 19823454	A1	19991125	DE 1998-19823454	19980518	
AU 9948968	A1	19991206	AU 1999-48968	19990517	<--

PRIORITY APPLN. INFO.:
DE 1998-19823454 19980518 <--
WO 1999-DE1524 19990517 <--

AB Disclosed is a method for photolithog. prodn. of oligonucleotides on two-dimensional matrixes for the prodn. of so-called DNA, PNA or **protein chips** by using dynamically controlled liq. crystal masks as photolithog. masks. The invention also relates to a device for implementing said method. The liq. crystal masks are formed for removal of the protective groups by irradn. Computer program is used for the process control of the photochem. solid phase synthesis according to the biosequence at the different spots.

=> d ibib abs hitstr 2

L42 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:45060 HCAPLUS
DOCUMENT NUMBER: 130:106052
TITLE: Isolation, cloning, and expression of rat aquaporin-5 (AQP5)
INVENTOR(S): Agre, Peter C.
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: U.S., 47 pp., Cont.-in-part of U.S. Ser. No. 930,168, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5858702	A	19990112	US 1995-393996	19950224 <--
US 5741671	A	19980421	US 1995-468763	19950606 <--

PRIORITY APPLN. INFO.:
US 1991-806273 19911213 <--
US 1992-930168 19920817 <--
US 1991-806723 19911212 <--
US 1995-393996 19950224 <--

AB Provided are the transmembrane water channel protein Aquaporin-5 (AQP5) and its methods of isolation, cloning, and expression. The mol. pathways through which salivary and lacrimal glands secrete water have yet been explained, and none of the previously known members of the Aquaporin family have been identified as existing at these locations nor in large airway epithelium. The present invention, however, implicates AQP5 in the generation of saliva, tears, and pulmonary secretions. The amino acid sequence of the protein has been deduced from the cDNA, and using the nucleic acid or protein sequence provided herein, the protein may be produced by recombinant DNA techniques. Expression of the protein may be detd. by either immunoassay or in situ hybridization assay. Also provided are synthetically produced liposomes contg. AQP5 and uses of the invention for screening potentially useful pharmacol. agonists/antagonists of the water channel. In addn. to rat AQP5, human AQP1 is also provided.

REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d kwic 2

L42 ANSWER 2 OF 3 HCAPLUS COPYRIGHT 2002 ACS
PRAI US 1991-806273 19911213 <--
US 1992-930168 19920817 <--
US 1991-806723 19911212 <--
US 1995-393996 19950224 <--
DT **Patent**
IT 146410-94-8P, **Protein CHIP** 28 (human clone pPCR-2/pCHIP precursor reduced) 164205-33-8P
RL: ARG (Analytical reagent use); BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); USES (Uses)
(amino acid sequence; cloning and expression of rat aquaporin-5 and human aquaporin-1)

=> d ibib abs hitstr 3

L42 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:250665 HCAPLUS
DOCUMENT NUMBER: 128:291153
TITLE: Isolation, cloning, sequence, and expression of human transmembrane water channel aquaporin 1 (AQP1) and rat aquaporin 5
INVENTOR(S): Agre, Peter C.
PATENT ASSIGNEE(S): Johns Hopkins University, USA
SOURCE: U.S., 48 pp. Division of U.S. Ser. No. 393,996.
CODEN: USXXAM
DOCUMENT TYPE: **Patent**
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5741671	A	19980421	US 1995-468763	19950606 <--
US 5858702	A	19990112	US 1995-393996	19950224 <--

PRIORITY APPLN. INFO.:
US 1991-806723 19911212 <--
US 1992-930168 19920817 <--
US 1995-393996 19950224 <--
US 1991-806273 19911213 <--

AB A transmembrane water channel protein is isolated in highly purified form from human erythrocytes. An identical protein is also found in kidney tubules. CDNA encoding this protein has been isolated and its amino acid sequence detd. CDNA encoding a transmembrane water channel protein has also been obtained from salivary gland, and an identical protein is found in lacrimal gland, cornea, and lung tissue. The amino acid sequence of the protein has been deduced from the cDNA, and the protein has been designated Aquaporin-5. Using the nucleic acid or protein sequence provided herein, the protein may be produced by recombinant DNA techniques. Expression of the protein may be detd. by either immunoassay or in situ hybridization assay.

=> d kwic 3

L42 ANSWER 3 OF 3 HCAPLUS COPYRIGHT 2002 ACS
PRAI US 1991-806723 19911212 <--
US 1992-930168 19920817 <--
US 1995-393996 19950224 <--
US 1991-806273 19911213 <--
DT **Patent**
IT 146410-94-8, **Protein CHIP** 28 (human clone pPCR-2/pCHIP precursor reduced) 164205-33-8
RL: PRP (Properties)
(amino acid sequence; isolation, cloning, sequence, and expression of human transmembrane water channel aquaporin 1 (AQP1) and rat aquaporin 5)

WPIDS record of inventor's work

TRAN 09/849,781

=> d bib abs

L51 ANSWER 1 OF 1 WPIDS COPYRIGHT 2002 DERWENT INFORMATION LTD
AN 2002-075172 [10] WPIDS
DNC C2002-022394
TI Positionally addressable array useful for detecting protein-probe interaction, comprises proteins, molecules comprising domains of proteins, whole cells or protein-containing cellular materials on a **solid support**.
DC B04 D16
IN KLEMIC, J F; REED, M; SNYDER, M; ZHU, H
PA (UYYA) UNIV YALE
CYC 95
PI WO 2001083827 A1 20011108 (200210)* EN 69p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
ADT WO 2001083827 A1 WO 2001-US14526 20010504
PRAI US 2000-221034P 20000727; US 2000-201921P 20000504
AN 2002-075172 [10] WPIDS
AB WO 200183827 A UPAB: 20020213
NOVELTY - A positionally addressable **array** (or **protein chip**) (I), comprises a number of substances (S) selected from proteins, molecules comprising functional domains of the proteins, whole cells or protein-containing cellular materials, on a **solid support**, with each substance being at a different position on the support, where (S) contains at least 100 different substances **per cm2**.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an array (II) comprising a number of wells on the surface of a **solid support**, where the density of the wells is at least 100 wells/cm2;

(2) making (I) comprising a number of wells on the surface of a **solid support**, by:

(a) **casting** an array from a microfabricated **mold** designed to produce a density of wells on a solid surface of greater than 100 wells/cm2, and optionally, depositing (S) in wells on a **solid support**, with each different substance being in a different well on the **solid support**; or

(b) **casting** a secondary **mold** from a microfabricated **mold** designed to produce a density of wells on a solid surface of greater than 100 wells/cm2 and **casting** at least one array from the secondary **mold**, and optionally, depositing (S) in wells on a **solid support**, with each different substance being in a different well on the **solid support**;

(3) a kit (K) comprising:

(a) one or more arrays comprising a number of wells on the surface of a **solid support**, where the density of the wells is at least 100 wells/cm2, and in one or more containers, one or more probes, reagents and other molecules; or

(b) one or more positionally addressable arrays comprising (S), and in one or more containers, one or more probes, reagents and other molecules;

USE - (I) is useful for detecting protein/probe interaction, by contacting (I) with a probe and detecting protein/probe interaction by

mass spectrometry, chemiluminescence, fluorescence, radiolabeling and atomic force microscopy. The probe is a substrate or inhibitor of kinases, phosphatases, proteases, glycosidases, acetylases and other group transferring enzymes, and is chosen from proteins, oligonucleotides, polynucleotides, DNA, RNA, small molecule substrates, drug candidates, receptors, antigens, steroids, phospholipids, antibodies, glutathione, immunoglobulin domains, maltose, nickel, dihydrotrypsin and biotin.

(I) is also useful for identifying an antigen that activates a lymphocyte, by contacting (I) with a number of lymphocytes derived from a patient, where (I) comprises a number of potential antigens (e.g., pathogens, antigens of autologous tissues, tissue-specific antigens, disease-specific antigens and synthetic antigens) on a **solid support**, and detecting positions on the **solid support** where lymphocyte activation occurs comprising:

(a) measuring antibody synthesis;

(b) measuring the incorporation of 3H-thymidine by a lymphocyte;

(c) determining the expression of cell surface molecules induced or suppressed by lymphocyte activation;

(d) determining the expression of secreted molecules induced by lymphocyte activation;

(e) or by measuring the release of 51Chromium.

(I) is also useful for determining the specificity of an antibody preparation comprising antiserum, monoclonal antibody, polyclonal antibody, Fab fragments, chimeric, humanized, single chain or synthetic antibodies, by contacting (I) comprising a number of potential antigens on a **solid support** with an antibody preparation, and detecting positions on the **solid support**, where binding by an antibody in the antibody preparation occurs, by contacting (I) with a fluorescently labeled secondary antibody that binds to the antibody in the preparation, removing unbound secondary antibody, and detecting bound label on the array.

(I) is also useful for identifying a mitogen, contacting (I) with a population of cells, and detecting positions on the **solid support**, where the mitogenic activity is induced in a cell (all claimed).

ADVANTAGE - The protein chips are cheap and have time advantage over the conventional protein chips. A large-scale parallel analysis for the presence, amount and/or functionality of the proteins can be performed. The chip is suitable for simultaneous identification of many protein-probe interactions and for determination of relative affinity to the interactions. The chip is also capable of detecting interactions in a milieu more representative of that in a cell and simultaneously evaluating many potential ligands. The chips are suitable for high density and small volume chemical reactions.

The use of wells as compared to prior art use of flat surface arrays eliminates or reduces the likelihood of cross-examination with respect to the contents of the wells, and has increased signal-to-noise ratios. Wells allow the use of larger volumes of reaction solution in a denser configuration, and hence greater signal is possible.

Moreover, the wells decrease the rate of evaporation, of the reaction solution from the chip as compared to flat surface arrays, thus allowing longer reaction times. The use of wells permits association studies using a fixed, limited amount of probe for each well on the chip, where the use of flat surfaces usually involves indiscriminate probe application across the whole substrate, and limits the detection of other probes in the mixture. The amount of probe applied to the individual protein is controlled and the probe can be different for different proteins.
Dwg.0/7

=> d bib abs 169

L69 ANSWER 1 OF 4 USPATFULL
AN 2002:27106 USPATFULL
TI Microarrays and their manufacture by slicing
IN Anderson, Norman G., Rockville, MD, UNITED STATES
Anderson, N. Leigh, Washington, DC, UNITED STATES
Braatz, James A., Beltsville, MD, UNITED STATES
PI US 2002015952 A1 20020207
AI US 2001-774794 A1 20010201 (9)
RLI Continuation-in-part of Ser. No. US 2000-628339, filed on 28 Jul 2000, PENDING Continuation-in-part of Ser. No. US 2000-482460, filed on 13 Jan 2000, PENDING
PRAI US 1999-146653P 19990730 (60) <--
DT Utility
FS APPLICATION
LREP Roylance, Abrams, Berdo & Goodman, L.L.P., Suite 600, 1300 19th Street, N.W., Washington, DC, 20036
CLMN Number of Claims: 80
ECL Exemplary Claim: 1
DRWN 8 Drawing Page(s)
LN.CNT 3164
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Microarrays are prepared by using a separate fiber for each compound being used in the microarray. The fibers are bundled and sectioned to form a thin microarray that may be glued to a backing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic

L69 ANSWER 1 OF 4 USPATFULL
PRAI US 1999-146653P 19990730 (60) <--
SUMM [0016] The invention also relates to methods for arranging the fibers to form bundles in which the **position** of each fiber relative to all others is retained throughout the bundle length.
DETD . . . depend on many factors, including, but not limited to, porosity of the strand, molecular size of the biological target molecule, **concentration** of the biological target molecule, temperature etc. After the strand is loaded with biological target molecule, the strand is washed. . .
DETD . . . Brief exposure of the cut surface of a chip to a solvent will dissolve some of the inclusions, increasing the **surface area** of the support plastic containing the agents of interest. In another embodiment, the material between the fibers can be removed,. . .
DETD . . . (Braatz et al., U.S. Pat. No. 5,169,720 and Braatz, J. Biomaterials Applications 9:71-96 (1994)). Alternatively, a bundled array may be **positioned** so that individual hollow fibers may be filled with biopolymers in solutions that gel prior to sectioning.
DETD [0092] In a related aspect, the channels can also vary in inner **surface area**. In a preferred embodiment, the inner **surface area** of the channels is from about 100 to about 1000 times the cross-sectional area of the group of channels. In one embodiment, the inner **surface area** of the channels has a range of between about 100 .mu.m.sup.2 to about 1.times.10.sup.3 .mu.m.sup.2. In another embodiment, the inner **surface area** of the channels has a range of between about 50 .mu.m.sup.2 to about 5.times.10.sup.3 .mu.m.sup.2. In a

preferred embodiment, the. . .

DETD [0151] When one wishes to enhance binding between analyte and binding partners on the **surface area** of particles in a fiber of the microarray, one may etch the embedding matrix of each fiber, thereby exposing more of the **surface area** of particles in each fiber of the microarray.

DETD . . . the fiber, sectioning through the porous particle or threadlike component may make the resulting structure more porous and allow greater **surface area** contact to both reagents and washing. Etching of an embedding medium or capillary also increases porosity and exposure to the. . .

DETD . . . find matching antibodies on the array. Then the bound analyte may be detected by scanning for fluorescence and identified by **position**.

DETD . . . wherein, for example, particles are embedded in a matrix to form a fiber, a filling material to maintain the relative **positioning** of the fibers along the length of the bundle may be desirable. Various glues and adhesives are known in the. . .

DETD . . . an internal quality assurance check for the array. Additionally, it is preferred for some of the cells to provide different **concentrations** of the binding component for quantitative measurement of an analyte. Those provide internal standards for the microarray for both qualitative detection and quantitative detection. For example, a series of cells may contain different **concentrations** of an antibiotic. When a sample microorganism is contacted with the cells and allowed to incubate, the absence of growth in one cell and the presence of growth in another cell provide an approximate minimal inhibitory **concentration**. The same can be done for determining minimal bacteriocidal **concentrations** when stained with a vital dye such as trypan blue or fluorescein acetate. Since a microarray may contain thousands of. . .

DETD . . . are preferably resistant to deformation, and in which each strand or capillary is continuous from one to the other. The **positional** arrangement of fibers or capillaries should remain the same throughout the bundle. Filaments composed of two different types of material. . .

DETD . . . diverse material. Partial dissolving to yield a porous material is also part of the instant invention. Porous materials have increased **surface area**, which is particularly desirable for binding assays.

DETD . . . array elements 41, and with a barcode 42 printed along one border to provide identification and orientation. In addition, small **concentrations** of dyes, usually non-fluorescent, may be incorporated into the polymers from which selected tubes are made such that they present. . .

DETD . . . at a time at one end of the bundle may be illuminated, and the light detected and related to array **position** at the other at the other end as shown in FIG. 6 where bundle 50 with fibers 51 is illuminated. . .

DETD . . . of two or more components. The fibers may act as light pipes or total internal reflection fiber optics to transmit **positional** alignment and information regarding chemical and biological reactions occurring on the surface. The fiber material preferably is chosen to support. . .

DETD . . . 1,000, 5,000, 10,000, 100,000 or a million or more cells per square centimeter of array. That is a much higher **concentration** than depositable cells formed by microfluidics in commercial microarrays.

DETD [0213] High **concentrations** of cells (sectors) in a microarray have been achieved using photolithography where the molecule of interest

is synthesized on the. . .

DETD . . . particular centrifuge tubes of stepped decreasing diameter from the open end to the closed end of the tube that enable **concentration** of desired low **concentration** biological elements in a small volume following appropriate methods of centrifugation. See, for example, W099/46047. Thus, microbes from biological samples,. . . allowed to find matching antibodies on the array. They then may be detected by scanning for fluorescence and identified by **position**. It is equally a part of the instant invention to immobilize microorganisms or other molecules of interest in the described. . .

DETD [0234] The previous methodology for preparation of **protein chips** requires preparation, use and reuse of large numbers of proteins in solution. Proteins, nucleic acids, biological cells, other chemicals and. . . unstable and deteriorate over time. Even if frozen, repeated use may involve repeated freeze-thaw cycles that denature certain proteins as **well**. By contrast, immobilized proteins have been shown to be stable over long periods of time.

DETD . . . supernatant protein and unreacted dye placed in a centrifugal protein concentrator, where the protein was washed by repeated dilution and re-**concentration** in buffer. The fluid was centrifuged to remove the Cellite and supernatant recentrifuged with 4 ml sodium bicarbonate buffer until. . .

DETD . . . two specifically labeled filaments were diagonally opposite one another in the 2.times.2 array, which was consistent with the diagonally opposite **positions** of the anti-HSA and mixed anti-HSA, Tf and Hp agarose filaments.

DETD . . . rat and mouse liver mitochondria, lysosomes and expressed proteins are suspended or dissolved in an aqueous buffer, at 10 mg/ml **concentration**, and optionally fixed with glutaraldehyde (1%). One ml of each preparation is mixed according to the kit instructions with 20. . .

DETD . . . suspension of the bacterial cells (other microorganisms, animal or plant cells are equally applicable) and are diluted to an approximate **concentration** of 20,000 cells/ml of culture medium. About 0.1 ml of the suspension is applied to the surface of the GCA.. . .

DETD . . . with nutrient agar mixed with various antibiotics in the following configuration. Five two-fold dilutions across the effective spectrum of useful **concentrations** of the antibiotics, erythromycin, penicillin V, tetracycline, ampicillin, trimethoprim/sulfamethiozole, cefaclor, ofloxacin and nitrofurantonin and 10 two-fold dilutions of 34 new. . .

DETD . . . with increases in trypan blue absorbance from the beginning to 30 minutes were considered to have dead cells. Minimal inhibitory **concentrations** (MIC's) and minimal bactericidal **concentrations** (MBC's) thus were determined. The possible effectiveness of the new candidate compounds likewise was deduced.

CLM What is claimed is:

1. A fiber bundle comprising a plurality of fibers attached to each other in a fixed **position** with respect to each other wherein the fibers have different agents of interest immobilized in or on different fibers.

8. The fiber bundle according to claim 1 wherein different fibers contain different **concentrations** of the agent of interest.

. . . claim 1 and cutting the fiber bundle transversely or at an angle to form a section such that the fixed **position** with respect to each other is maintained.

. . . bundling said plurality of fibers in a predetermined arrangement; bonding or fixing said bundled plurality of fibers to fix the **positions** of the fibers; and cleaving said bundled fibers into a plurality of chips to be deposited at a specific address. . .

=> d bib abs l69 2

L69 ANSWER 2 OF 4 USPATFULL
AN 2001:205574 USPATFULL
TI Microarrays and their manufacture
IN Anderson, Norman G., Rockville, MD, United States
Anderson, N. Leigh, Washington, DC, United States
PI US 2001041339 A1 20011115
AI US 2001-880019 A1 20010614 (9)
RLI Division of Ser. No. US 2000-482460, filed on 13 Jan 2000, PENDING
PRAI US 1999-146653P 19990730 (60) <--
DT Utility
FS APPLICATION
LREP ROYLANCE, ABRAMS, BERRO & GOODMAN, L.L.P., 1300 19TH STREET, N.W., SUITE 600, WASHINGTON,, DC, 20036
CLMN Number of Claims: 50
ECL Exemplary Claim: 1
DRWN 8 Drawing Page(s)
LN.CNT 2244
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The microarrays of the present invention are prepared by using a separate fiber for each compound being used in the microarray. The fibers are bundled and sectioned to form a thin microarray that is glued to a backing.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs l69 3

L69 ANSWER 3 OF 4 USPATFULL
AN 2001:134012 USPATFULL
TI Retentate chromatography and **protein chip** **arrays** with applications in biology and medicine
IN Hutchens, T. William, Los Altos, CA, United States
Yip, Tai-Tung, Cupertino, CA, United States
PA Ciphergen Biosystems, Inc. (U.S. corporation)
PI US 2001014461 A1 20010816
AI US 2000-745388 A1 20001221 (9)
RLI Division of Ser. No. US 1998-100302, filed on 19 Jun 1998, GRANTED, Pat. No. US 6225047
PRAI US 1997-54333P 19970620 (60) <--
US 1997-67484P 19971201 (60) <--
DT Utility
FS APPLICATION
LREP TOWNSEND AND TOWNSEND AND CREW, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
CLMN Number of Claims: 30
ECL Exemplary Claim: 1
DRWN 44 Drawing Page(s)
LN.CNT 4314
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods of retentate chromatography for resolving analytes in a sample. The methods involve adsorbing the analytes to a substrate under a plurality of different selectivity conditions, and detecting the analytes retained on the substrate by desorption spectrometry. The methods are useful in biology and medicine, including clinical diagnostics and drug discovery.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 3

L69 ANSWER 3 OF 4 USPATFULL
TI Retentate chromatography and **protein chip** **arrays** with applications in biology and medicine
PRAI US 1997-54333P 19970620 (60) <--
PRAI US 1997-67484P 19971201 (60) <--
DETD . . . attached to a first substrate to provide a solid phase, such as a polymeric or glass bead, which is subsequently **positioned** on a second substrate which functions as the means for presenting the sample to the desorbing energy of the desorption. . .
DETD . . . be suitable for mounting in a horizontally and/or vertically translatable carriage that horizontally and/or vertically moves the substrate to successively **position** each predetermined addressable location of adsorbent in a path for interrogation by the energy source and detection of the analyte. . .
DETD [0171] The sample containing the analyte may be contacted to the adsorbent either before or after the adsorbent is **positioned** on the substrate using any suitable method which will enable binding between the analyte and the adsorbent. The adsorbent can. . .
DETD . . . For example, various bases of attraction between the eluant and the analyte include charge or pH, ionic strength, water structure, **concentrations** of specific competitive binding reagents, surface tension, dielectric constant and combinations of two or more of the above.

DETD . . . Eluants which modify the selectivity of the adsorbent with respect to ionic strength include salt solutions of various types and **concentrations**. The amount of salt solubilized in the eluant solution affects the ionic strength of the eluant and modifies the adsorbent binding ability correspondingly. Eluants containing a low **concentration** of salt provide a slight modification of the adsorbent binding ability with respect to ionic strength. Eluants containing a high **concentration** of salt provide a greater modification of the adsorbent binding ability with respect to ionic strength.

DETD [0244] Eluants which modify the selectivity of the adsorbent by alteration of water structure or **concentration** include urea and chaotropic salt solutions. Typically, urea solutions include, e.g., solutions ranging in **concentration** from 0.1 to 8 M. Chaotropic salts which can be used to provide eluants include sodium thiocyanate. Water structure-based eluants. . .

DETD . . . another format for presentation. Data analysis can include the steps of determining, e.g., signal strength as a function of feature **position** from the data collected, removing "outliers" (data deviating from a predetermined statistical distribution), and calculating the relative binding affinity of. . .

DETD [0464] Add 1-5 .mu.l of sample to each spot. For samples with very low antigen or ligand **concentration**, put the adsorbent array into a bioprocessor. Wash the spots on the chip and Bioprocessor wells with 200 .mu.l PBS. . .

DETD . . . agent, (e.g., acetonitrile) in the selectivity threshold modifier decreases the retention of lysozyme on the hydrophobic C.sub.3 adsorbent. The acetonitrile **concentration** range for elution of lysozyme from the hydrophobic C.sub.3 adsorbent is between 20-50%. Including detergent (Tween20), or urea, in the. . .

DETD . . . alone. Including a polarity modulating agent, (e.g., acetonitrile) in the selectivity threshold modifier decreases the retention of lysozyme. The acetonitrile **concentration** range for elution of lysozyme from the hydrophobic C.sub.3 adsorbent is between 20-50%, however, when the lysozyme peak intensities retained. .

DETD . . . profile shows the lysozyme signal intensity retained on the anionic adsorbent after washing with pH 7 buffer alone. Including increasing **concentrations** of sodium chloride (0.1-0.4 M) in the selectivity threshold modifier decreases the retention of lysozyme. This indicates that the interaction of lysozyme (a basic protein) with the anionic adsorbent involves an ion exchange mechanism. A 0.4 M NaCl **concentration** is required to elute the lysozyme. Lowering the pH of the selectivity threshold modifier to pH 4.5 in the sodium. . .

DETD . . . different breast cancer cell lines are cultured for the same period of time in a constant composition culture medium. After **concentration** with a filtration unit, an aliquot of 1 .mu.l of each culture medium is added to various spots of a. . .

DETD [0633] A specific binding of M13 phage displaying single chain antibody against Tat protein was observed in a **concentration** dependent manner (solid line). FIGS. 26A-26D. Nonspecific binding by a nonspecific M13 phage was minimal on the adsorbent array (dashed. . .

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DETD . . . Eluants which modify the selectivity of the adsorbent with respect to ionic strength include salt solutions of various types and **concentrations**. The amount of salt solubilized in the eluant solution affects the ionic strength of the eluant and modifies the adsorbent binding ability correspondingly. Eluants containing a low **concentration** of salt provide a slight modification of the adsorbent binding ability with respect to ionic strength. Eluants containing a high **concentration** of salt provide a greater modification of the adsorbent binding ability with respect to ionic strength.

DETD [0244] Eluants which modify the selectivity of the adsorbent by alteration of water structure or **concentration** include urea and chaotropic salt solutions. Typically, urea solutions include, e.g., solutions ranging in **concentration** from 0.1 to 8 M. Chaotropic salts which can be used to provide eluants include sodium thiocyanate. Water structure-based eluants. . .

DETD . . . another format for presentation. Data analysis can include the steps of determining, e.g., signal strength as a function of feature **position** from the data collected, removing "outliers" (data deviating from a predetermined statistical distribution), and calculating the relative binding affinity of. . .

DETD [0464] Add 1-5 .mu.l of sample to each spot. For samples with very low antigen or ligand **concentration**, put the adsorbent array into a bioprocessor. Wash the spots on the chip and Bioprocessor wells with 200 .mu.l PBS. . .

DETD . . . agent, (e.g., acetonitrile) in the selectivity threshold modifier decreases the retention of lysozyme on the hydrophobic C.sub.3 adsorbent. The acetonitrile **concentration** range for elution of lysozyme from the hydrophobic C.sub.3 adsorbent is between 20-50%. Including detergent (Tween20), or urea, in the. . .

DETD . . . alone. Including a polarity modulating agent, (e.g., acetonitrile) in the selectivity threshold modifier decreases the retention of lysozyme. The acetonitrile **concentration** range for elution of lysozyme from the hydrophobic C.sub.3 adsorbent is between 20-50%, however, when the lysozyme peak intensities retained. .

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DETD . . . different breast cancer cell lines are cultured for the same period of time in a constant composition culture medium. After **concentration** with a filtration unit, an aliquot of 1 .mu.l of each culture medium is added to various spots of a. . .

DETD [0633] A specific binding of M13 phage displaying single chain antibody against Tat protein was observed in a **concentration** dependent manner (solid line). FIGS. 26A-26D. Nonspecific binding by a nonspecific M13 phage was minimal on the adsorbent array (dashed. . .

=> d bib abs 169 4

L69 ANSWER 4 OF 4 USPATFULL
AN 2001:128549 USPATFULL
TI Dry deposition of materials for microarrays using matrix displacement
IN Anderson, Norman G., Rockville, MD, United States
Anderson, N. Leigh, Washington, DC, United States
Braatz, James A., Beltsville, MD, United States
PI US 2001012537 A1 20010809
AI US 2001-772974 A1 20010131 (9)
RLI Continuation-in-part of Ser. No. US 2000-628339, filed on 28 Jul 2000, PENDING Continuation-in-part of Ser. No. US 2000-482460, filed on 13 Jan 2000, PENDING
PRAI US 1999-146653P 19990730 (60) <--
DT Utility
FS APPLICATION
LREP Dean H. Nakamura, Roylance, Abrams, Berdo & Goodman, L.L.P., Suite 600, 1300 19th Street, N.W., Washington, DC, 20036
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 1963
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A method is disclosed which relates to the placement of binding partners on microarrays, where such binding partners contain proteins, nucleic acids, biological cells and other bio-reactive components. The present invention discloses uses and methods for manufacture of microarrays constructed in part by sectioning bundles of tubules or rods containing matrix immobilized bio-reactive molecules to produce large numbers of sample chips. The chips so produced are processed by deposition to microarrays. The deposited chips can then be manipulated to partition the immobilizing matrix away from the bio-reactive molecules contained in the matrix and to place said partitioned molecules onto various surfaces for subsequent analysis, to include binding assays, hybridization reactions, diagnostic methods and a variety of cell interaction-determining methodologies.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 4

L69 ANSWER 4 OF 4 USPATFULL
PRAI US 1999-146653P 19990730 (60) <--
SUMM . . . technology feeds off the methods evolved in the electronics industry and therefore has some of the same requirements, vis, accurate **positioning** to micron scales, clean room requirements and the use of multiple photo-masks to define the array pattern. Although electronic "chips". . .
SUMM . . . the number of chips on a wafer (the substrate on which multiple arrays are produced) results in an increase in **surface area**, which increases demand on the chemicals used in photochemistry (assuming no change in chip size).
SUMM . . . each element of the array over time. By preparing a microarray with the same immobilized compound or component in different **concentrations**, a more quantative result may be obtained. As the present invention permits a greater range of amounts to be deposited on a unit of **surface area**, a more sensitive and wider sensitivity range may be achieved.

DETD [0050] The term "uniformly distributed" refers to a substantially equal **concentration** of bio-reactive components within a defined analysis field (area).

DETD . . . solid surface may have a considerably larger range of protein density. The same applies different amounts of fluid and different **surface areas** and for any other agents of interest and the solid cylinder may be of almost any height.

DETD . . . materials. Brief exposure of the surface of a chip to a solvent will dissolve some of these inclusions, increasing the **surface area** of the support material containing the agents of interest and allowing them to adhere to the solid surface directly or. . .

DETD . . . embedded within the fiber, sectioning through the porous particle or threadlike component may make it more porous and allow greater **surface area** contact to both reagents and washing. Etching of an embedding medium or capillary also increases porosity and exposure to the. . .

DETD . . . a solid phase or forming a compound at each cell. The former technique is limited by the spill, maximum practical **concentration** and ability to quantitatively measure small quantities of liquid. The later technique is limited by the types of different compounds. . .

DETD . . . to find their matching antibodies on the array. They may then be detected by scanning for fluorescence and identified by **position.**

DETD . . . an internal quality assurance check for the array. Additionally, it is preferred for some of the cells to provide different **concentrations** of the binding component for quantitative measurement of an analyte. These provide internal standards for the microarray for both qualitative detection and quantitative detection. For example, a series of cells may contain different **concentrations** of an antigens left by their gel fibers. When a sample antibody is contacted with the cells and allowed to. . . of binding signal in another cell provide an approximate binding affinity. The same can be done for determining minimal bacteriocidal **concentrations** when stained with a vital dye such as trypan blue or fluorescein acetate. Since a microarray may contain thousands of. . .

DETD . . . are preferably resistant to deformation, and in which each strand or capillary is continuous from one to the other. The **positional** arrangement of fibers or capillaries should remain the same throughout the bundle. Filaments composed of two different types of material. . .

DETD . . . have machine readable indicia such as a barcode printed along one border to provide identification and orientation. In addition, small **concentrations** of dyes, usually non-fluorescent, may be incorporated into the polymers from which selected tubes are made such that they present. . .

DETD . . . at a time at one end of the bundle may be illuminated, and the light detected and related to array **position** at the other at the other end.

DETD . . . of two or more components. The fibers may act as light pipes or total internal reflection fiber optics to transmit **positional** alignment and information regarding chemical and biological reactions occurring on the surface.

DETD . . . 1,000, 5,000, 10,000, 20,000, 100,000 or a million or more cells per square centimeter of array. These are much higher **concentrations** than depositable cells formed by microfluidics in commercial microarrays.

DETD . . . to find their matching antibodies on the array. They may then be detected by scanning for fluorescence and identified by

position. It is equally a part of the present invention to immobilize microorganisms or other molecules of interest in the described. . .

DETD [0168] The previous methodology for preparation of **protein chips** requires preparation, use and reuse of large numbers of proteins in solution. Proteins, nucleic acids, biological cells, other chemicals and. . . unstable and deteriorate over time. Even if frozen, repeated use may involve repeated freeze-thaw cycles that denature certain proteins as **well**. By contrast, immobilized proteins have been shown to be stable over long periods of time.

DETD . . . supernatant protein and unreacted dye placed in a centrifugal protein concentrator, where the protein is washed by repeated dilution and re-**concentration** in buffer. The fluid is centrifuged to remove the Cellite and supernatant recentrifuged with 4 ml sodium bicarbonate buffer until. . .

DETD . . . rat and mouse liver mitochondria, lysosomes, and expressed proteins are suspended or dissolved in an aqueous buffer, at 10 mg/ml **concentration**, and optionally fixed with glutaraldehyde (1%). 1 ml of each preparation is mixed with low temperature gelling agarose. The mixture. . .

CLM What is claimed is:

7. The method of claim 1, wherein said placing step (1) comprises **positioning** said solid on at least one porous membrane which abuts said at least one surface.

KWIC display for some patents in L62 & L69 is given

=> d ti pn 1-14

L62 ANSWER 1 OF 14 USPATFULL
TI Expression monitoring for gene function identification
PI US 2002028454 A1 20020307

L62 ANSWER 2 OF 14 USPATFULL
TI Methods of array synthesis
PI US 2002022721 A1 20020221

L62 ANSWER 3 OF 14 USPATFULL
TI Determining signal transduction pathways
PI US 6340565 B1 20020122

L62 ANSWER 4 OF 14 USPATFULL
TI PSCA: Prostate stem cell **antigen** and uses thereof
PI US 2001055751 A1 20011227

L62 ANSWER 5 OF 14 USPATFULL
TI Exploiting genomics in the search for new drugs
PI US 6333155 B1 20011225

L62 ANSWER 6 OF 14 USPATFULL
TI Nucleic acid affinity columns
PI US 2001053526 A1 20011220

L62 ANSWER 7 OF 14 USPATFULL
TI Methods and compositions for amplifying detectable signals in specific binding assays
PI US 2001041335 A1 20011115

L62 ANSWER 8 OF 14 USPATFULL
TI Method for comparing copy number of nucleic acid sequences
PI US 6309822 B1 20011030

L62 ANSWER 9 OF 14 USPATFULL
TI Expression monitoring for gene function identification
PI US 6303301 B1 20011016

L62 ANSWER 10 OF 14 USPATFULL
TI Nucleic acid affinity columns
PI US 6280950 B1 20010828

L62 ANSWER 11 OF 14 USPATFULL
TI Methods and compositions for amplifying detectable signals in specific binding assays
PI US 6203989 B1 20010320

L62 ANSWER 12 OF 14 USPATFULL
TI Chemical amplification for the synthesis of patterned arrays
PI US 6083697 20000704

L62 ANSWER 13 OF 14 USPATFULL
TI Nucleic acid affinity columns
PI US 6013440 20000111

L62 ANSWER 14 OF 14 USPATFULL
TI Removal of cells from an aqueous suspension
PI US 5191068 19930302
WO 9007715 19900712

=> d bib abs 1

L62 ANSWER 1 OF 14 USPATFULL
AN 2002:48263 USPATFULL
TI Expression monitoring for gene function identification
IN Mack, David, Menlo Park, CA, UNITED STATES
PI US 2002028454 A1 20020307
AI US 2001-836278 A1 20010418 (9)
RLI Division of Ser. No. US 1998-86285, filed on 29 May 1998, GRANTED, Pat. No. US 6303301 Continuation-in-part of Ser. No. WO 1998-US1206, filed on 12 Jan 1998, UNKNOWN
PRAI US 1997-35327P 19970113 (60) <--
DT Utility
FS APPLICATION
LREP BANNER & WITCOFF, LTD., ELEVENTH FLOOR, 1001 G STREET, N.W., WASHINGTON, DC, 20001-4597
CLMN Number of Claims: 128
ECL Exemplary Claim: 1
DRWN 21 Drawing Page(s)
LN.CNT 3041
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods, compositions and apparatus for mapping the regulatory relationship among genes by massive parallel monitoring gene expression. In some embodiments, mutations in the up-stream regulatory genes are detected by monitoring the change in down-stream gene expression. Similarly, the function of a specific mutation in a up-stream gene is determined by monitoring the down-stream gene expression. In addition, regulatory function of a target gene can be determined by monitoring the expression of a large number of down-stream genes. The invention also provides specific embodiments for detecting p53 functional homozygous and heterozygous mutations and for determining the function of p53 mutations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 1

L62 ANSWER 1 OF 14 USPATFULL
PRAI US 1997-35327P 19970113 (60) <--
SUMM . . . example, p53 can be functionally rather than genetically inactivated by binding to viral proteins, such as E1B and large T **antigen**. By assaying for the ability of a regulatory protein to activate or repress other gene's expression, the both genetic and. . .
DETD [0067] The terms "nucleic acid" or "nucleic acid molecule" refer to a deoxyribonucleotide or ribonucleotide **polymer** in either single-or double-stranded form, and unless otherwise limited, would encompass analogs of natural nucleotide that can function in a. . .
DETD . . . embodiment using high density arrays, high density oligonucleotide arrays are synthesized using methods such as the Very Large Scale Immobilized **Polymer** Synthesis (VLSIPS) disclosed in U.S. Pat. No. 5,445,934 incorporated herein for all purposes by reference. Each oligonucleotide occupies a known. . .
DETD . . . than 65,000 or 250,000 or even greater than about 1,000,000 different oligonucleotide probes, preferably in less than 1 cm.sup.2 of **surface area**. The oligonucleotide probes range from about 5 to about 50 or about 500 nucleotides, more preferably from about 10 to. . .
DETD [0155] Methods of forming **high density**

arrays of oligonucleotides, **peptides** and other **polymer** sequences with a minimal number of synthetic steps are known. The oligonucleotide analogue array can be synthesized on a solid. . . using, for example, light-directed synthesis techniques. See also, Fodor et al., Science, 251, 767-77 (1991). These procedures for synthesis of **polymer** arrays are now referred to as VLSIPS.TM. procedures. Using the VLSIPS.TM. approach, one heterogeneous array of **polymers** is converted, through simultaneous coupling at a number of reaction sites, into a different heterogeneous array. See, U.S. application Ser.. . .

DETD . . . proceeds using automated phosphoramidite chemistry and chip masking techniques. In one specific implementation, a glass surface is derivatized with a **silane** reagent containing a functional group, e.g., a hydroxyl or amine group blocked by a photolabile protecting group. Photolysis through a. . .

DETD . . . "flow channel" method applied to the compounds and libraries of the present invention can generally be described as follows. Diverse **polymer** sequences are synthesized at selected regions of a substrate or **solid support** by forming flow channels on a surface of the substrate through which appropriate reagents flow or in which appropriate reagents. . .

DETD . . . the ability to detect genetic variation across a large number of genes and to correlate genetic factors with the resulting **cellular** consequences. The use of **high density** oligonucleotide (nucleic acid) **arrays** provided genotyping of candidate genes as well as the characterization of the relative abundance of mRNAs identified herein. Information from. . .

DETD . . . critical intermediates between upstream RTKs (21, 22) and GPCRs (23, 24), and downstream signaling components involved in cellular transformation (including **mitogen** activated protein (MAPK) kinases); see Van Biesen, T., Hawes, B. E., Luttrell, D. K., Krueger, K. M., Touhara, K., Porfiri,. . . receptor tyrosine kinases to Ras signalling, Nature 6424, 85-88 (1993); Howe, L. R., Marshall & C. J. Lysophosphatidic acid stimulates **mitogen**-activated protein kinase activation via a G-protein-coupled pathway requiring p21ras and p74raf-1. Journal of Biological Chemistry 28, 20717-20720 (1993); and Alblas, J., Van Corven, E. J., Hordijk, P. L., Milligan, G. & Moolenaar, W. H. Gi-mediated activation of the p21ras-**mitogen**-activated protein kinase pathway by alpha 2-adrenergic receptors expressed in fibroblasts. Journal of Biological Chemistry 30, 22235-22238 (1993). Although Ras mutations. . . 133-144 (1995)). The concurrent up-regulation of RTKs and down-regulation of caveolins in BT474 strongly indicate a convergence of multiple upstream **mitogenic** signaling events on the Ras pathway in this breast carcinoma. Interestingly, our analysis also revealed up-regulation of Ras, Raf, Mek. . .

CLM What is claimed is:

61. The method of claim 46 wherein the nucleic acid probes are attached to a **solid support**.

85. The method of claim 71 wherein the nucleic acid probes are attached to a **solid support**.

99. A **solid support** comprising an array of nucleic acid probes, wherein at least 50 of said probes comprise a portion of at least. . .

100. The **solid support** of claim 99 wherein at least 75 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .

101. The **solid support** of claim 99 wherein at least

100 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .
102. The **solid support** of claim 99 wherein at least 150 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .
103. The **solid support** of claim 99 wherein at least 200 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .
104. The **solid support** of claim 99 wherein at least 250 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .
105. The **solid support** of claim 99 wherein at least 300 of said probes comprise a portion of at least 9 contiguous nucleotides of. . .
106. The **solid support** of claim 99 comprising probes selected from those shown in Table 2.

=> d bib abs 2

L62 ANSWER 2 OF 14 USPATFULL
AN 2002:38001 USPATFULL
TI Methods of array synthesis
IN Trulson, Mark, San Jose, CA, UNITED STATES
McGall, Glenn, Mountain View, CA, UNITED STATES
Fidanza, Jacqueline, San Francisco, CA, UNITED STATES
PA Affymetrix, INC. (U.S. corporation)
PI US 2002022721 A1 20020221
AI US 2001-922426 A1 20010803 (9)
PRAI US 2000-223290P 20000803 (60)
US 1996-30826P 19961114 (60) <--
DT Utility
FS APPLICATION
LREP AFFYMETRIX, INC, ATTN: CHIEF IP COUNSEL, LEGAL DEPT., 3380 CENTRAL EXPRESSWAY, SANTA CLARA, CA, 95051
CLMN Number of Claims: 79
ECL Exemplary Claim: 1
DRWN 7 Drawing Page(s)
LN.CNT 1603
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Radiation-activated catalysts (RACs), autocatalytic reactions, and protective groups are employed to achieve a highly sensitive, high resolution, radiation directed combinatorial synthesis of pattern arrays of diverse **polymers**. When irradiated, RACs produce catalysts that can react with enhancers, such as those involved in autocatalytic reactions. The autocatalytic reactions produce at least one product that removes protecting groups from synthesis intermediates. This invention has a wide variety of applications and is particularly useful for the solid phase combinatorial synthesis of **polymers**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 2

L62 ANSWER 2 OF 14 USPATFULL
PRAI US 1996-30826P 19961114 (60) <--
AB . . . protective groups are employed to achieve a highly sensitive, high resolution, radiation directed combinatorial synthesis of pattern arrays of diverse **polymers**. When irradiated, RACs produce catalysts that can react with enhancers, such as those involved in autocatalytic reactions. The autocatalytic reactions. . . intermediates. This invention has a wide variety of applications and is particularly useful for the solid phase combinatorial synthesis of **polymers**.
SUMM . . . processes. In particular, embodiments of the present invention are directed to novel methods and compositions for synthesizing arrays of diverse **polymer** sequences, such as polypeptides and polynucleotides. According to a specific aspect of the invention, a method of synthesizing diverse **polymer** sequences, such as peptides or polynucleotides, is provided. The diverse **polymer** sequences are useful, for example, in nucleic acid analysis, gene expression monitoring, receptor and nucleic acid binding studies, surface based. . .
SUMM [0004] Improved methods of forming **high-density arrays** of **peptides**, polynucleotides, and other **polymer** sequences in a short period of time have been devised

using combinatorial solid phase synthesis. See Kozal et al., Nature. . . . all purposes. Known methods of synthesizing high-density arrays employ radiation-labile protecting groups and photolithographic masks to achieve spatially defined combinatorial **polymer** synthesis on a substrate surface. In those embodiments, masks are used to control the selective exposure to radiation in specific. . . . monomer is then coupled to the unprotected linker molecules. The process can be repeated to synthesize a large number of **polymer** sequences in specific locations.

SUMM [0005] Other methods for synthesizing high-density **polymer** arrays employ blocks containing channels for reagent delivery at preselected sites on the substrate. See U.S. Pat. No. 6,040,193, incorporated. . . . certain embodiments, a block is contacted with the substrate and the reagents necessary to form a portion of the immobilized **polymer** are permitted to access the substrate via the channel(s). The block or substrate can be rotated and the process repeated to form arrays of **polymers** on the substrate. The block channel method can be combined with light-directed methodologies.

SUMM . . . . Certain embodiments of the present invention provide novel methods, compositions, and devices useful in synthesizing novel high-density arrays of diverse **polymer** sequences. The **polymer** sequences are fashioned from individual synthesis intermediates and include diverse naturally or non-naturally occurring peptides, nucleotides, polypeptides or polynucleotides.

SUMM . . . . novel chemical amplification process using a catalyst system which is initiated by radiation to assist in the synthesis of the **polymer** sequences as well as the use of photosensitive compounds which act as catalysts to chemically alter the synthesis intermediates in a manner to promote formation of **polymer** sequences. Such photosensitive compounds include what are generally referred to as radiation-activated catalysts (RACs), and more specifically photo activated catalysts. . . .

SUMM [0011] The present invention is advantageous because it makes possible the synthesis of **polymers** of any desired chemical sequence at known locations on a substrate with high synthesis fidelity, small synthesis features, and improved. . . .

SUMM [0012] One embodiment of the present invention provides methods of manufacturing high-density **polymer** arrays using chemical amplification techniques. The present invention also provides methods of manufacturing **polymer** arrays using less time and lower radiation intensities to improve **polymer** purity, to improve the spatial resolution and contrast between **polymer** and substrate and to decrease the area on the substrate where **polymer** sequences can be synthesized allowing many and different **polymer** sequences on the same substrate. The present invention also improves precision, contrast, and ease of manufacture in the production of **polymer** arrays.

DETD . . . . monomer is a member of the set of small molecules which are or can be joined together to form a **polymer** or a compound composed of two or more members. The set of monomers includes but is not restricted to, for. . . . set of which is readily known to those of skill in the art. The particular ordering of monomers within a **polymer** is referred to herein as the "sequence" of the **polymer**. As used herein, "monomers" refers to any member of a basis set for synthesis of a **polymer**, and is not limited to a single "mer". For example, dimers of the 20 naturally occurring L-amino acids form a basis set of 400 monomers for synthesis of polypeptides. Monomers can also include trimers, oligomers, **polymers** and so forth. Different basis sets of monomers may be used at successive steps in the synthesis of a **polymer**. Furthermore, each of the sets

may include protected members, which are modified after synthesis. The invention is described herein primarily. . . of molecules containing sequences of monomers such as nucleic acids, but could readily be applied in the preparation of other **polymers**. Such **polymers** include, for example, both linear and cyclic **polymers** of nucleic acids, polysaccharides, phospholipids, and peptides having either .alpha.-, .beta.-, or .gamma.-amino acids, heteropolymers in which a known drug is covalently bound to any of the above, polynucleotides, polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyethyleneimines, polyarylene sulfides, **polysiloxanes**, polyimides, polyacetates, or other **polymers** which will be apparent upon review of this disclosure. Such **polymers** are "diverse" when **polymers** having different monomer sequences are formed at different predefined regions of a substrate. Methods of cyclization and **polymer** reversal of **polymers** are disclosed in co-pending application Ser. No. 796,727, filed Nov. 22, 1991, entitled "**POLYMER** REVERSAL ON SOLID SURFACES," incorporated herein by reference for all purposes.

DETD [0033] A peptide is a **polymer** in which the monomers are .alpha.-amino acids and are joined together through amide bonds, alternatively referred to as a polypeptide.. . .

DETD . . . by this invention include, but are not restricted to, antibodies, cell membrane receptors, monoclonal antibodies and antisera reactive with specific **antigenic** determinants, viruses, cells, drugs, polynucleotides, nucleic acids, peptides, cofactors, lectins, sugars, polysaccharides, cellular membranes, and organelles. Receptors are sometimes referred. . .

DETD . . . in investigating a receptor that comprises a ligand-binding site on an antibody molecule which combines with an epitope of an **antigen** of interest; analyzing a sequence that mimics an **antigenic** epitope may lead to the development of vaccines in which the immunogen is based on one or more of such. . .

DETD [0045] **Polymers**, preferably polypeptides, which are capable of promoting a chemical reaction involving the conversion of one or more reactants to one. . .

DETD [0051] A material having a rigid or semi-rigid surface usually made from glass or suitable **polymer** materials. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different **polymers** with, for example, wells, raised regions, etched trenches, or the like. In some embodiments, the substrate itself contains wells, trenches,. . .

DETD . . . 4-methoxybenzenesulfonyl, 4-methoxybenzyl, 4-methylbenzyl, o-nitrophenylsulfenyl, 2-phenyl-2-propyloxycarbonyl, .alpha.-2,4,5-tetramethylbenzyloxycarbonyl, p-toluenesulfonyl, xanthenyl, benzyl ester, N-hydroxysuccinimide ester, p-nitrobenzyl ester, p-nitrophenyl ester, phenyl ester, p-nitrocarbonate, p-nitrobenzylcarbonate, **trimethylsilyl** and pentachlorophenyl ester and the like.

DETD . . . area on a substrate. In a particularly preferred embodiment it is intended to be used for formation of a selected **polymer**. It is otherwise referred to herein in the alternative as "reaction" region, a "selected" region, or simply a "region." The. . . e.g., circular, rectangular, elliptical, wedge-shaped, etc. In some embodiments, a predefined region and, therefore, the area upon which each distinct **polymer** sequence is synthesized is smaller than about 1 mm.sup.2, more preferably less than 1 cm.sup.2, and still more preferably less. . . regions have an area less than about 10,000 .mu.m.sup.2 or, more preferably, less than 100 .mu.m.sup.2. Within these regions, the **polymer** synthesized therein is preferably

synthesized in a substantially pure form.

DETD [0057] A **polymer** is considered to be "substantially pure" within a predefined region of a substrate when it exhibits characteristics that distinguish it. . . . that the predominant species in the predefined region is the desired sequence. According to preferred aspects of the invention, the **polymer** is at least 5% pure, more preferably more than 10% to 20% pure, more preferably more than 95% pure, where purity for this purpose refers to the ratio of the number of **polymer** molecules formed in a predefined region having a desired sequence to the total number of molecules formed in the predefined. . .

DETD . . . based computation. The present invention provides methods, devices, and compositions for the formation of arrays of large numbers of different **polymer** sequences. The methods and compositions provided herein involve the conversion of radiation signals into chemical products in an amplified manner that is particularly useful in **polymer** synthesis. The invention also includes the arrays formed using the methods and compositions disclosed herein. One aspect of the invention includes methods, compositions, and devices for the synthesis of an array of different **polymers** in selected and predefined regions of a substrate. Another aspect of the invention includes those arrays and various methods of. . .

DETD [0073] In a preferred embodiment using microarray technology on a substrate, nucleic acids or other **polymers** with different sequences can be immobilized, each in a predefined area on a surface. In some embodiments, such immobilized nucleic. . . the substrate. The nucleic acids of a particular sequence are provided within a predefined region of a substrate, having a **surface area**, for example, of about 1 cm.sup.2 to 10.sup.-10 cm.sup.2. In some embodiments, the regions have areas of less than about. . . exceeding about 400 different nucleic acids/cm.sup.2, wherein each of the different nucleic acids is attached to the surface of the **solid support** in a different predefined region, has a different determinable sequence, and is, for example, at least 4 nucleotides in length.. . . of different nucleic acids may be, for example, 1000 or more. Further discussion on arrays of nucleic acids or other **polymers** immobilized on a surface are described in detail in U.S. Pat. No. 5,744,305, the disclosure of which is incorporated herein.

DETD . . . given monomer. By repeatedly activating different sets of predefined regions and providing different monomer compositions thereto, a diverse array of **polymers** is produced on or near the substrate. Other regions of the substrate remain inactive because they are blocked by the. . .

DETD . . . has a protective group that can be removed in a subsequent reaction step. In this stepwise manner, diverse arrays of **polymers** are synthesized at preselected regions of a substrate.

DETD . . . and 6,083,697, previously incorporated herein by reference. In the radiation-directed methods described in the '854 patent, the surface of a **solid support**, optionally modified with spacers having photolabile protecting groups such as NVOC or MeNPOC, is illuminated through a photolithographic mask, yielding. . . (which is carried out by the above methods). Alternatively, a library of probes can be prepared by first derivatizing a **solid support** with multiple poly(A) or poly(T) oligonucleotides which are suitably protected with photolabile protecting groups, deprotecting at known sites and constructing. . .

DETD [0079] According to one embodiment of the presently claimed invention, spatially defined **polymer** synthesis will be performed by depositing a photoresist such as those used extensively in the semiconductor industry, more fully discussed. . . the substrate

available for coupling. These steps of depositing resist, selectively removing resist and monomer coupling are repeated to form **polymers** of desired sequence at desired locations.

DETD [0080] In some specific embodiments, a positive-tone resist comprised of diazonapthoquinone-novolac (DNQ/N) is incorporated in a cresol-formaldehyde **polymer** matrix. This resist and its variants are used routinely in the microelectronics industry for submicron resolution lithography, as more fully discussed in Reiser, "Photoreactive **Polymers**: the Science and Technology of Resists", Wiley (1989), incorporated herein by reference in its entirety for all purposes. High contrast. . . the alkaline conditions needed to develop the DNQ/N resists (aqueous [OH.sup.-]>0.1 M) complicates its direct use in a multi-step **polymer** synthesis, such as the polynucleotide array fabrication process, because of the hydrolysis of akali-labile nucleobase protecting groups that are used. . .

DETD . . . exposed in a non-linear process. A number of compounds suitable for CELs have been described and include, for example, nitrones, **polysilanes**, diazonium salts, diazo analogs, alkalines such as tetramethylammonium hydroxide (TMAH), "D6", pyrylium dyes, and "built-on-mask" (BOM) material. (See, for example,. . . Introduction to Microlithography; American Chemical Society, 1994, incorporated herein by reference in its entirety for all purposes.) The use of **polysilanes** as a resist material for CEL is described in Hofer et al., "Contrast enhanced uv lithography with **polysilanes**" SPIE Vol. 469 Advances in Resist Technology 108-116 (1984), and West et al., "Contrast Enhanced Photolithography: Application of Photobleaching Processes. . .

DETD . . . invention, rather than depositing the CEL on a photoresist layer, the CEL is deposited directly on the photoprotected substrate or **polymer** layer prior to each synthesis step. The CEL is first coated on the photoprotected substrate and may be reapplied between. . .

DETD . . . the fabrication of high-density probe arrays. A glass substrate 106 comprising a synthesis intermediate to which are attached monomers and **polymers** 108 and protecting groups 104 is coated with a CEL 100 comprising a photobleachable dye. A mask 102 comprising light. . .

DETD . . . containing a removable protective group for reaction with exposed functional groups. This process is repeated to selectively apply monomers until **polymers** of a desired length and desired chemical sequence are obtained. Protective groups are then optionally removed and the sequence is,. . .

DETD . . . for reaction and includes dimethoxytrityl, MeNPOC, tert-butyloxycarbonyl or any of the protecting groups previously identified; R.sub.2 is cyanoethyl, methyl, t-butyl, **trimethylsilyl** and the like; R.sub.3 and R.sub.4 are isopropyl, cyclohexone and the like; and R.sub.5 is hydrogen, NR'R", OR, SR, CRR'R",. . .

DETD . . . or the like. Of course, the substrate may be made from any one of a variety of materials such as **silicon**, polystyrene, polycarbonate, or the like. In operation, the surface of the substrate is appropriately treated by cleaning with, for example,. . . containing from 2-10 monomers or more, diamines, diacids, amino acids, or combinations thereof. In some embodiments the surface may be **silanated**. Thereafter, the surface is provided with protected surface active groups such as tertbutyloxycarbonyl (TBOC) or fluorenylmethoxycarbonyl (FMOC) protected amino acids.. . .

DETD [0121] The significantly enhanced resolution made possible by the present invention permits the synthesis of more **polymers** on a given **surface area**. Therefore, the invention can be

used for building chemical libraries and screening for biological activities of a large number of. . .

DETD [0128] A MeNPOC monomer was covalently attached to a **solid support**. A CEM layer comprising diazonium dye was then spincoated on the **solid support**. The surface was baked at 85.degree. C. for 3 minutes. The support was then selectively deprotected by irradiation through a. . .

DETD . . . (FSI). The "MeNPOC only" serves as the baseline, thus the maximum FSI is approximately 10000 units. The curves of the " **polymer** alone" and the "MeNPOC control with **polymer**" are nearly identical to that of the "MeNPOC only" curve, thus indicating that the latency effect is not created by addition of the **polymer**, but is rather due to the addition of the dye. The FSI for the 5% solution reached nearly 9000 units. . .

DETD . . . as a function of the irradiation dose. In traditional photo resists, this nonlinearity stems from the solubility behavior of the **polymer**. Although the catalytic photo process described in this application does not involve a development step, nonlinear behavior was observed. This. . .

DETD . . . C. for 2 min, irradiated with varying doses at 365 nm, and postbaked at 85.degree. C. for 2 min. The **polymer** coating was then removed with an acetone wash and the surface treated with a fluorescent coupling reagent. As shown by. . . in a decrease in the contrast. The contrast was calculated using the contrast equation as defined in Reiser, Arnost, Photoreactive **Polymers**: the Science and Technology of Resists, pp. 226-228 (1989), incorporated in its entirety herein by reference for all purposes.

DETD [0136] The presently claimed invention provides greatly improved methods for synthesizing arrays of diverse **polymer** sequences. Many variations of the invention will be apparent to those of skill in the art upon reviewing the above. . .

CLM What is claimed is:

9. A method for synthesizing **polymers** of diverse sequences comprising the steps of: a) forming a surface comprising a protective group; b) coating said surface with. . .

33. A method for synthesizing a **polymer** array on a substrate comprising the steps of: a) providing a layer on the surface of the substrate having one. . . reactive group protected from reaction by a protective group; f) repeating steps a through e, or not, until a desired **polymer** sequence is obtained.

46. A method for synthesizing **polymers** of diverse sequences comprising the steps of: a) forming a surface comprising a photosenstive protecting group b) coating said surface. . .

47. A method for synthesizing **polymers** of diverse sequences comprising the steps of: a) providing a first surface comprising a photosensitive compound or group; b) providing. . .

56. A method for synthesizing a **polymer** array on a substrate comprising the steps of: a) forming a surface having one or more synthesis intermediates bound thereon,. . . if another synthesis intermediate is to be added; and g) repeating steps b) through f) or not, until a desired **polymer** sequence is obtained.

57. A method for synthesizing a **polymer** array on a substrate comprising the steps of: a) forming a first surface having one or more synthesis intermediates bound. . . compound, if another synthesis intermediate is to be added h) repeating steps b) through h) or not, until a desired **polymer** sequence is obtained.

=> d bib abs 3

L62 ANSWER 3 OF 14 USPATFULL
AN 2002:13886 USPATFULL
TI Determining signal transduction pathways
IN Oliner, Jonathan D., Newbury, CA, United States
Hubbell, Earl, Los Angles, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6340565 B1 20020122
AI US 1999-431964 19991101 (9)
PRAI US 1998-106912P 19981103 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: McGarry, Sean; Assistant Examiner: Shibuya, Mark
LREP Banner & Witcoff, Ltd.
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 1796
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Experimental and analytical methods enable reconstruction of signal transduction networks from gene expression profiles. Signal transduction pathways can be reverse-engineered by 1) experimentally manipulating individual genes, 2) generating cellular expression profiles, and 3) analyzing for common patterns among these profiles. Analysis of patterns among profiles permits reconstruction of pathways and networks of interrelationships among genes and their products.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 3

L62 ANSWER 3 OF 14 USPATFULL
PRAI US 1998-106912P 19981103 (60) <--
DETD . . . gene. Expression profiles for thousands of genes can be obtained simultaneously by hybridizing labeled RNA (or derived cDNA) from these **cell** lines to **high-density** oligonucleotide **arrays**. Other methods known in the art for obtaining expression data of multiple genes can also be used, including the Serial. . .
DETD . . . embodiments using high density arrays, high density oligonucleotide arrays are synthesized using methods such as the Very Large Scale Immobilized **Polymer** Synthesis (VLSIPS) disclosed in U.S. Pat. No. 5,445,934 incorporated herein for all purposes by reference. Each oligonucleotide occupies a known. . .
DETD . . . than 65,000 or 250,000 or even greater than about 1,000,000 different oligonucleotide probes, preferably in less than 1 cm.sup.2 of **surface area**. The oligonucleotide probes range from about 5 to about 50 or about 500 nucleotides, more preferably from about 10 to. . .
DETD Methods of forming **high density arrays** of oligonucleotides, **peptides** and other **polymer** sequences with a minimal number of synthetic steps are known. The oligonucleotide analogue array can be synthesized on a solid. . . using, for example, light-directed synthesis techniques. See also, Fodor et al., Science, 251, 767-77 (1991). These procedures for synthesis of **polymer** arrays are now referred to as VLSIPS.TM. procedures. Using the VLSIPS.TM. approach, one heterogeneous array of

polymers is converted, through simultaneous coupling at a number of reaction sites, into a different heterogeneous array. See, U.S. application Ser.. . .

DETD . . . proceeds using automated phosphoramidite chemistry and chip masking techniques. In one specific implementation, a glass surface is derivatized with a **silane** reagent containing a functional group, e.g., a hydroxyl or amine group blocked by a photolabile protecting group. Photolysis through a. . .

DETD . . . "flow channel" method applied to the compounds and libraries of the present invention can generally be described as follows. Diverse **polymer** sequences are synthesized at selected regions of a substrate or **solid support** by forming flow channels on a surface of the substrate through which appropriate reagents flow or in which appropriate reagents. . .

DETD . . . B., O'Connor, P. M., and Fornace, A. J., Jr. (1994). "Interaction of the p53-regulated protein Gadd45 with proliferating cell nuclear **antigen**." Science, 266(5189), 1376-80.

=> d bib abs 4

L62 ANSWER 4 OF 14 USPATFULL
AN 2001:237635 USPATFULL
TI PSCA: Prostate stem cell **antigen** and uses thereof
IN Reiter, Robert E, Los Angeles, CA, United States
Witte, Owen N, Sherman Oaks, CA, United States
Saffran, Douglas C, Los Angeles, CA, United States
Jakobovits, Aya, Beverly Hills, CA, United States
PI US 2001055751 A1 20011227
AI US 2000-564329 A1 20000503 (9)
RLI Continuation-in-part of Ser. No. US 1999-359326, filed on 20 Jul 1999, PENDING Continuation-in-part of Ser. No. US 1999-318503, filed on 25 May 1999, GRANTED, Pat. No. US 6261791 Continuation-in-part of Ser. No. US 1999-251835, filed on 17 Feb 1999, GRANTED, Pat. No. US 6261789 Continuation-in-part of Ser. No. US 1998-203939, filed on 2 Dec 1998, GRANTED, Pat. No. US 6258939 Continuation-in-part of Ser. No. US 1998-38261, filed on 10 Mar 1998, GRANTED, Pat. No. US 6267960
PRAI US 1997-228816P 19970310 (60) <--
US 1998-71141P 19980112 (60) <--
US 1998-74675P 19980213 (60) <--
US 1998-113230P 19981221 (60) <--
US 1999-120536P 19990217 (60) <--
US 1999-124658P 19990316 (60) <--
DT Utility
FS APPLICATION
LREP Mandel & Adriano, 35 N Arroyo Parkway Suite 60, Pasadena, CA, 91103
CLMN Number of Claims: 52
ECL Exemplary Claim: 1
DRWN 79 Drawing Page(s)
LN.CNT 5004
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a novel prostate cell-surface **antigen**, designated Prostate Stem Cell **Antigen** (PSCA), which is widely over-expressed across all stages of prostate cancer, including high grade prostatic intraepithelial neoplasia (PIN), androgen-dependent and androgen-independent prostate tumors.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 4

L62 ANSWER 4 OF 14 USPATFULL
TI PSCA: Prostate stem cell **antigen** and uses thereof
PRAI US 1997-228816P 19970310 (60) <--
PRAI US 1998-71141P 19980112 (60) <--
PRAI US 1998-74675P 19980213 (60) <--
PRAI US 1998-113230P 19981221 (60) <--
PRAI US 1999-120536P 19990217 (60) <--
PRAI US 1999-124658P 19990316 (60) <--
AB The invention provides a novel prostate cell-surface **antigen**, designated Prostate Stem Cell **Antigen** (PSCA), which is widely over-expressed across all stages of prostate cancer, including high grade prostatic intraepithelial neoplasia (PIN), androgen-dependent and.
. .
SUMM [0006] Recently, there has been a particularly strong interest in identifying cell surface tumor-specific **antigens** which might be useful as targets for various immunotherapeutic or small molecule

treatment strategies. A large number of such cell-surface **antigens** have been reported, and some have proven to be reliably associated with one or more cancers. Much attention has been focused on the development of novel therapeutic strategies which target these **antigens**. However, few truly effective immunological cancer treatments have resulted.

SUMM [0007] The use of monoclonal antibodies to tumor-specific or over-expressed **antigens** in the treatment of solid cancers is instructive. Although antibody therapy has been well researched for some 20 years, only. . . Herceptin, recently approved for use in the treatment of metastatic breast cancers overexpressing the HER2/neu receptor. Another is the human/mouse **chimeric** anti-CD20/B cell lymphoma antibody, Rituxan, approved for the treatment of non-Hodgkin's lymphoma. Several other antibodies are being evaluated for the treatment of cancer in clinical trials or in pre-clinical research, including a **chimeric** and a fully human IgG2 monoclonal antibody specific for the epidermal growth factor receptor (Slovin et al., 1997, Proc. Am.. . . is finally emerging from a long embryonic phase. Nevertheless, there is still a very great need for new, more-specific tumor **antigens** for the application of antibody and other biological therapies. In addition, there is a corresponding need for tumor **antigens** which may be useful as markers for antibody-based diagnostic and imaging methods, hopefully leading to the development of earlier diagnosis. . .

SUMM [0011] There are some known markers which are expressed predominantly in prostate, such as prostate specific membrane **antigen** (PSM), a hydrolase with 85% identity to a rat neuropeptidase (Carter et al., 1996, Proc. Natl. Acad. Sci. USA 93:. . . for prostate cancer (Su et al., 1996). Vaccines for prostate cancer are also being actively explored with a variety of **antigens**, including PSM and PSA.

SUMM [0012] The invention provides a novel prostate cell-surface **antigen**, designated Prostate Stem Cell **Antigen** (PSCA), which is widely over-expressed across all stages of prostate cancer, including high grade prostatic intraepithelial neoplasia (PIN), androgen-dependent and androgen-independent prostate tumors. The PSCA gene shows 30% homology to stem cell **antigen**-2 (SCA-2), a member of the Thy-1/Ly-6 family of glycosylphosphatidylinositol (GPI)-anchored cell surface **antigens**, and encodes a 123 amino acid protein with an amino-terminal signal sequence, a carboxy-terminal GPI-anchoring sequence, and multiple N-glycosylation sites.. . .

DRWD [0018] FIG. 3. Alignment of amino acid sequences of human PSCA, murine PSCA, and human stem cell **antigen**-2 (hSCA-2). Shaded regions highlight conserved amino acids. Conserved cysteines are indicated by bold lettering. Four predicted N-glycosylation sites in PSCA. . .

DRWD [0065] FIG. 50. Schematic representations of PSCA Capture ELISA. (A) Standardization and control **antigens**: A GST-fusion protein encoding amino acids 18-98 of the PSCA protein is used for generating a standard curve for quantification. . .

DRWD . . . 1G8 on LAPC-9 and PC-3 prostate tumors is compared, showing no effect on PC-3 tumors, which do not express PSCA **antigen**, but significant growth inhibition in LAPC-9 tumors, which do express PSCA **antigen**. See Examples 18-C1, -C3 for details.

DETD [0089] The present invention relates to Prostate Stem Cell **Antigen** (hereinafter "PSCA"). PSCA is a novel, glycosylphosphatidylinositol (GPI)-anchored cell surface **antigen** which is expressed in normal cells such prostate cells, urothelium, renal collecting ducts, colonic neuroendocrine cells, placenta, normal bladder and. . .

DETD . . . contains an amino-terminal signal sequence, a carboxy-terminal GPI-anchoring sequence, and multiple N-glycosylation sites. PSCA shows

30% homology to stem cell **antigen**-2 (SCA-2), a member of the Thy-1/Ly-6 gene family, a group of cell surface proteins which mark the earliest phases of. . .

DETD [0105] The invention further provides antibodies (e.g., polyclonal, monoclonal, **chimeric**, and humanized antibodies) that bind to PSCA. The most preferred antibodies will selectively bind to PSCA and will not bind. . . antibodies that are particularly contemplated include monoclonal and polyclonal antibodies as well as fragments thereof (e.g., recombinant proteins) containing the **antigen** binding domain and/or one or more complement determining regions of these antibodies. These antibodies can be from any source, e.g.,. . .

DETD . . . as at least a portion of the variable region of the immunoglobulin molecule that binds to its target, i.e., the **antigen** binding region. Some of the constant region of the immunoglobulin may be included.

DETD [0114] **Chimeric** antibodies of the invention are immunoglobulin molecules that comprise a human and non-human portion. The **antigen** combining region (variable region) of a **chimeric** antibody can be derived from a non-human source (e.g. murine) and the constant region of the **chimeric** antibody which confers biological effector function to the immunoglobulin can be derived from a human source. The **chimeric** antibody should have the **antigen** binding specificity of the non-human antibody molecule and the effector function conferred by the human antibody molecule.

DETD [0115] In general, the procedures used to produce **chimeric** antibodies can involve the following steps:

DETD [0116] a) identifying and cloning the correct gene segment encoding the **antigen** binding portion of the antibody molecule; this gene segment (known as the VDJ, variable, diversity and joining regions for heavy. . .

DETD [0118] c) ligating the variable region with the constant region so that the complete **chimeric** antibody is encoded in a form that can be transcribed and translated;

DETD [0123] h) screening for cells expressing the desired **chimeric** antibody; and

DETD [0125] Antibodies of several distinct **antigen** binding specificities have been manipulated by these protocols to produce **chimeric** proteins [e.g. anti-TNP: Boulianne et al., Nature 312:643 (1984); and anti-tumor **antigens**: Sahagan et al., J. Immunol. 137:1066 (1986)]. Likewise, several different effector functions have been achieved by linking new sequences to those encoding the **antigen** binding region. Some of these include enzymes [Neuberger et al., Nature 312:604 (1984)], immunoglobulin constant regions from another species and. . . al., Nature 309:364 (1984); Tan et al., J. Immunol. 135:3565-3567 (1985)]. Additionally, procedures for modifying antibody molecules and for producing **chimeric** antibody molecules using homologous recombination to target gene modification have been described (Fell et al., Proc. Natl. Acad. Sci. USA. . .

DETD . . . cells, as is generally known. The immortalized cell lines secreting the desired antibodies are screened by immunoassay in which the **antigen** is the PSCA protein or PSCA fragment. When the appropriate immortalized cell culture secreting the desired antibody is identified, the. . .

DETD . . . Regions that bind specifically to the desired regions of the PSCA protein can also be produced in the context of **chimeric** or CDR grafted antibodies of multiple species origin. The invention includes an antibody, e.g., a monoclonal antibody which competitively inhibits. . .

DETD [0141] Reactivity of anti-PSCA mAbs against the target **antigen**

may be established by a number of well known means, including Western blot, immunoprecipitation, ELISA, and FACS analyses using, as. . .

DETD [0146] Additionally, the recombinant protein of the invention comprising the **antigen**-binding region of any of the monoclonal antibodies of the invention can be used to treat cancer. In such a situation, the **antigen**-binding region of the recombinant protein is joined to at least a functionally active portion of a second protein having therapeutic. . .

DETD [0151] The human PSCA gene maps to chromosome 8q24.2. Human stem cell **antigen** 2 (RIG-E), as well as one other recently identified human Ly-6 homologue (E48) are also localized to this region, suggesting. . .

DETD . . . of the PSCA ligand or other agent or constituent to bind to PSCA and/or the ability to inhibit/stimulate PSCA activity. **Assays** for PSCA activity (e.g., binding) using a PSCA **protein** are suitable for use in **high** through-**put** screening methods.

DETD . . . of the PSCA protein. As described above, antibodies are obtained by immunization of suitable mammalian subjects with peptides, containing as **antigenic** regions, those portions of the PSCA protein intended to be targeted by the antibodies. Critical regions may include the domains. . .

DETD . . . and quantitatively determining the concentration of PSCA in a biological fluid sample. In one embodiment the method comprises contacting a **solid support** with an excess of one or more monoclonal antibodies which forms (preferably specifically forms) a complex with PSCA under conditions permitting the monoclonal antibody to attach to the surface of the **solid support**. The resulting **solid support** to which the monoclonal antibody is attached is then contacted with a biological fluid sample so that the PSCA in. . .

DETD . . . preferred. Thus, the invention provides a method of treating a patient susceptible to or having a cancer which expresses PSCA **antigen**, comprising administering to said patient an effective amount of an antibody which binds specifically to the extracellular domain of PSCA.. . . mAbs may also be used in a method for selectively inhibiting the growth of or killing a cell expressing PSCA **antigen** comprising reacting a PSCA antibody immunoconjugate or immunotoxin with the cell in an amount sufficient to inhibit the growth of. . .

DETD [0211] For example, unconjugated PSCA antibody (including monoclonal, polyclonal, **chimeric**, humanized, fully human and fragments thereof (e.g., recombinant proteins)) may be introduced into a patient such that the antibody binds. . .

DETD . . . hormone-refractory metastatic prostate cancer. The 1G8 antibody is a mouse gamma-1, isotypic, neutral antibody, which interacts directly with the PSCA **antigen**. The 3C5 antibody is a mouse gamma-2A isotypic, antibody, which binds to cells and complement. Thus, the 1G8 antibody may. . .

DETD [0224] It should be noted that the use of murine or other non-human monoclonal antibodies and **chimeric** mAbs may induce moderate to strong immune responses in some patients. In the most severe cases, such an immune response. . . of the invention are those which are either fully human or humanized and which bind specifically to the target PSCA **antigen** with high affinity but exhibit low or no **antigenicity** in the patient.

DETD . . . of the mAb or mAbs used, the degree of PSCA expression in the patient, the extent of circulating shed PSCA **antigen**, the desired steady-state antibody concentration level, frequency of treatment, and the influence of chemotherapeutic agents used in

combination with the. . .

DETD . . . mAbs administered directly to bladder will be cleared from the patient rapidly, it may be possible to use non-human or **chimeric** antibodies effectively without significant complications of **antigenicity**.

DETD [0231] The invention further provides vaccines formulated to contain a PSCA protein or fragment thereof. The use of a tumor **antigen** in a vaccine for generating humoral and cell-mediated immunity for use in anti-cancer therapy is well known in the art. . .

DETD [0233] Various ex vivo strategies may also be employed. One approach involves the use of dendritic cells to present PSCA **antigen** to a patient's immune system. Dendritic cells express MHC class I and II, B7 costimulator, and IL-12, and are thus highly specialized **antigen** presenting cells. In prostate cancer, autologous dendritic cells pulsed with peptides of the prostate-specific membrane **antigen** (PSMA) are being used in a Phase I clinical trial to stimulate prostate cancer patients' immune systems (Tjoa et al.,. . .

DETD . . . Such an anti-idiotypic antibody can be used in anti-idiotypic therapy as presently practiced with other anti-idiotypic antibodies directed against tumor **antigens**.

DETD . . . invention further provides methods for inhibiting cellular activity (e.g., cell proliferation, activation, or propagation) of a cell expressing multiple PSCA **antigens** on its cell surface. This method comprises reacting the immunoconjugates of the invention (e.g., a heterogeneous or homogenous mixture) with the cell so that the PSCA **antigens** on the cell surface forms a complex with the immunoconjugates. The greater the number of PSCA **antigens** on the cell surface, the greater the number of PSCA-antibody complexes can be used. The greater the number of PSCA-antibody. . .

DETD [0239] In another embodiment, the invention provides methods for selectively inhibiting a cell expressing PSCA **antigen** by reacting any one or a combination of the immunoconjugates of the invention with the cell in an amount sufficient. . .

DETD . . . ability of this PSCA fragment to drive expression of an operatively linked transgene has been tested using a series of **chimeric** reporter constructs transfected into cells. The **chimeric** reporter constructs demonstrate an expression pattern similar to that of native endogenous PSCA, and the PSCA fragment drives expression of. . .

DETD . . . transcript and protein accumulation is known, and the PSCA upstream regulatory region has been isolated and characterized. A series of **chimeric** constructs comprising the PSCA upstream regulatory region operatively linked to a transgene has been tested. The PSCA upstream regulatory region. . .

DETD . . . Proc Natl Acad Sci USA 1982; 79:4927; Smith et al. infectious vaccinia virus recombinants that express hepatitis B virus surface **antigens**. Nature, 1983 302:490.)

DETD [0298] The interrelationship of dosages for animals of various sizes and species and humans based on mg/m.sup.2 of **surface area** is described by Freireich, E. J., et al. Cancer Chemother., Rep. 50 (4): 219-244 (1966). Adjustments in the dosage regimen. . .

DETD . . . be formulated within various lipid compositions, such as, for example, liposomes as well as in various polymeric compositions, such as **polymer** microspheres.

DETD Identification And Molecular Characterization Of A Novel Prostate Cell Surface **Antigen** (PSCA)

DETD . . . analysis revealed that clone #15 had no exact match in the databases, but shared 30% nucleotide homology with stem cell **antigen** 2, a member of the Thy-1/Ly-6 superfamily of glycosylphosphatidylinositol (GPI)-anchored cell surface

antigens. Clone #15 encodes a 123 amino acid protein which is 30% identical to SCA-2 (also called RIG-E) and contains a. . . Rev. Biochem. 64: 563-591). It also contains four predicted N-glycosylation sites. Because of its strong homology to the stem cell **antigen** -2, clone #15 was renamed prostate stem cell **antigen** (PSCA). 5' and 3' PCR RACE analysis was then performed using cDNA obtained from the LAPC-4 androgen independent xenograft and. . .

DETD . . . phospholipase C digestion for GPI-anchored proteins was confirmed by performing the same experiment on 293T cells transfected with the GPI-linked **antigen** CD59 or the non-GPI linked transmembrane protein E25a (Deleersnijder et al., 1996, J. Biol. Chem 271: 19475-19482). PLC digestion reduced. . .

DETD . . . Specimens obtained from UCLA were stained using modifications of an immunoperoxidase technique previously described (Said, J. W. et al., 1998). **Antigen** retrieval was performed on paraffin sections using a commercial steamer and 0.01M citrate buffer pH 6.0. After incubation with PSCA. . . stained as previously described using an automated Ventana NexES instrument (Ventana Medical Systems, Tucson, Ariz.) (Magi-Galluzzi, C. et al., 1997). **Antigen** retrieval was done by microwave for 15 min. in EDTA, pH 8.05 at 750W. mAbs purified at a concentration of. . .

DETD . . . biology and for potential clinical applications such as in vivo targeting applications is dependent on their ability to recognize the **antigen** of interest on the plasma membrane (Liu, H. et al., 1997; McLaughlin, P. et al., 1998; Wu, Y. et al.,. . .

DETD . . . induce tumor formation in prostate basal cells. As shown in FIG. 41, the strategy involves administration, e.g., microinjection, of a **chimeric** oncogene vector, comprising the upstream region of the PSCA gene operatively linked to a transgene that encodes a gene product. . .

DETD . . . tumor can be analyzed and compared with known characteristics of tumors caused by the particular oncogene used in constructing the **chimeric** oncogene vector. In addition, various tissues and organs of the transgenic mouse can be analyzed by DNA, RNA and proteins analyses to ascertain the presence and expression patterns of the **chimeric** oncogene vector.

DETD Transgenic Mice Carrying **Chimeric** Vectors Comprising hPSCA Upstream Sequences and a Transgene

DETD [0403] The expression patterns of transgenes under the control of hPSCA upstream regions will be tested. Toward this end, **chimeric** mice carrying **chimeric** vectors comprising hPSCA upstream sequences and a transgene have been generated. **Chimeric** vectors comprising 9 kb or 6 kb of hPSCA upstream sequences operatively linked to a transgene were constructed, and are. . . PSCA (6 kb)-GFP-3'hGH) (Brinster et al 1988 PNAS 85: 836-840), and the genomic fragment encoding SV40 small and large T **antigen** including an intron (PSCA (9 kb)-SV40TAG and PSCA (6 kb)-SV40TAG) (Brinster et al 1984 Cell 37:367-379).

DETD [0404] The **chimeric** vectors were used to generate a line of founder transgenic mice. Linearized **chimeric** vectors were microinjected into fertilized mouse eggs derived from intercrosses of C57BL/6X C3H hybrid mice. Founder mice that carried the **chimeric** vector were identified by Southern analysis of tail DNA, using GFP cDNA or SV40 genomic DNA as a probe. The. . .

DETD . . . on PSCA-expressing LAPC-9 xenografts. These results clearly show that the 1G8 antibody is inhibiting tumor cell growth through the PSCA **antigen**.

DETD . . . 1G8 are used as capture antibodies and are coated microtiter wells. After coating, incubation with a dilution series of test **antigen** is conducted in order to generate a standard curve.

Patient serum is added to the wells and incubated at room. . .
DETD [0457] A schematic representation of the standardization and control **antigens** are shown in FIG. 50A. Briefly, a GST-fusion protein encoding amino acids 18-98 of PSCA is used for generating a. . .
DETD . . . results, tabulated below (Table 5), show that 1G8 has a 1 nanomolar K.sub.D, indicating a strong affinity for the PSCA **antigen**.
TABLE 5

BIOCORE AFFINITY DETERMINATION OF PSCA mAb 1G8

##EQU2##
CLM What is claimed is:
6. An antibody, comprising an **antigen** binding site, wherein the **antigen** binding site recognizes and binds the N terminal region of PSCA.

7. An antibody, comprising an **antigen** binding site, wherein the **antigen** binding site recognizes and binds the C terminal region of PSCA.

8. An antibody, comprising an **antigen** binding site, wherein the **antigen** binding site recognizes and binds the middle region of PSCA.

11. A recombinant protein which is a murine/human **chimeric** antibody having (a) a variable region of the antibody of claim 1, 2, 3, 4, 5, 6, 7 or 8. . .
12. A polypeptide that binds PSCA comprising the **antigen** -binding region of the antibody of claim 1, 2, 3, 4, 5, 6, 7 or 8.

13. A monoclonal antibody, the **antigen**-binding region of which competitively inhibits the immunospecific binding of the antibody of claim 1, 2, 3, 4, 5, 6, 7 or 8 to its target **antigen**.

14. A bispecific antibody with a binding specificity for two different **antigens**, one of the **antigens** being that with which the antibody of claim 1, 2, 3, 4, 5, 6, 7, or 8 binds.

16. A single chain antibody molecule that binds PSCA comprising an **antigen** binding region of the antibody of claim 1, 2, 3, 4, 5, 6, 7 or 8.

25. A pharmaceutical composition useful in killing human cells expressing the PSCA **antigen** on the cell surface, comprising a pharmaceutically effective amount of the antibody of claim 1, 2, 3, 4, 5, 6,. . .
26. A pharmaceutical composition useful in killing human cells expressing the PSCA **antigen** on the cell surface, comprising a pharmaceutically effective amount of the immunoconjugate of any one of the claims 17-22, and. . .
27. A method for treating a subject suffering from a malignant disease characterized by cells having the PSCA **antigen** on the cell surface which comprises administering to the subject an effective amount of an immunoconjugate of any one of the claims 17-22 such that the immunoconjugate binds the PSCA **antigen** and kills said cells thereby treating the subject.

35. The method of claim 29, wherein the monoclonal antibody comprises murine **antigen** binding region residues and human antibody residues.

=> d bib abs 5

L62 ANSWER 5 OF 14 USPATFULL
AN 2001:235088 USPATFULL
TI Exploiting genomics in the search for new drugs
IN Lockhart, David J., Del Mar, CA, United States
Wodicka, Lisa, San Diego, CA, United States
Ho, Ming Hsiu, San Jose, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6333155 B1 20011225
AI US 1998-215207 19981218 (9)
PRAI US 1997-68289P 19971219 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Fredman, Jeffrey; Assistant Examiner: Chakrabarti, Arun Kr.
LREP Banner & Witcoff
CLMN Number of Claims: 14
ECL Exemplary Claim: 1
DRWN 11 Drawing Figure(s); 6 Drawing Page(s)
LN.CNT 1865
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The cellular effects of potentially therapeutic compounds are characterized in mammalian cells and yeast. In the latter case the effects can be characterized on a genome-wide scale by monitoring changes in messenger RNA levels in treated **cells** with **high-density** oligonucleotide probe **arrays**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 5

L62 ANSWER 5 OF 14 USPATFULL
PRAI US 1997-68289P 19971219 (60) <--
AB . . . latter case the effects can be characterized on a genome-wide scale by monitoring changes in messenger RNA levels in treated **cells** with **high-density** oligonucleotide probe **arrays**.
DETD . . . or solid phase. Preferably the assays are done on a solid phase. More preferably the probes are bound to a **solid support** which is an array. Any number of probes can be used which specifically hybridize to genes which are affected by. . .
DETD . . . 15, 17, 21, 25 or 30 nucleotides. Probes are desirably labeled with a moiety which is either radioactive, enzymatically detectable, **antigenically** detectable, or fluorometrically detectable.
DETD . . . object. These may be on an array or in a kit together. They are typically separated, either spatially on a **solid support** such as an array, or in separate vessels, such as vials or tubes. According to the present invention, at least. . .
DETD Nucleic Acid: The terms "nucleic acid" or "nucleic acid molecule" refer to a deoxyribonucleotide or ribonucleotide **polymer** in either single-or double-stranded form, and unless otherwise limited, would encompass analogs of natural nucleotide that can function in a. . .
DETD . . . embodiment using high density arrays, high density oligonucleotide arrays are synthesized using methods such as the Very Large Scale Immobilized **Polymer** Synthesis (VLSIPS) disclosed in U.S. Pat. No. 5,445,934 incorporated herein for all purposes by reference. Each oligonucleotide occupies a known. . .

DETD . . . than 65,000 or 250,000 or even greater than about 1,000,000 different oligonucleotide probes, preferably in less than 1 cm.sup.2 of **surface area**. The oligonucleotide probes range from about 5 to about 50 or about 500 nucleotides, more preferably from about 10 to. . .

DETD Methods of forming **high density arrays** of oligonucleotides, **peptides** and other **polymer** sequences with a minimal number of synthetic steps are known. The oligonucleotide analogue array can be synthesized on a solid. . . using, for example, light-directed synthesis techniques. See also, Fodor et al., Science, 251, 767-77 (1991). These procedures for synthesis of **polymer** arrays are now referred to as VLSIPS.TM. procedures. Using the VLSIPS.TM. approach, one heterogeneous array of **polymers** is converted, through simultaneous coupling at a number of reaction sites, into a different heterogeneous array. See, U.S. application Ser.. . .

DETD . . . proceeds using automated phosphoramidite chemistry and chip masking techniques. In one specific implementation, a glass surface is derivatized with a **silane** reagent containing a functional group, e.g., a hydroxyl or amine group blocked by a photolabile protecting group. Photolysis through a. . .

DETD . . . "flow channel" method applied to the compounds and libraries of the present invention can generally be described as follows. Diverse **polymer** sequences are synthesized at selected regions of a substrate or **solid support** by forming flow channels on a surface of the substrate through which appropriate reagents flow or in which appropriate reagents. . .

DETD . . . reductive amination, and Suzuki coupling reactions (6). During library synthesis, one position is held invariant to allow attachment to the **solid support**. Libraries are synthesized in a spatially separated format with either a pin apparatus (7) or polystyrene resin and screened for. . .

DETD . . . conformations (FIG. 2). Purvalanol B fits snugly into the ATP-binding site, as is evident by the 86% complementarity between the **surface area** buried by the inhibitor (364 .ANG..sup.2) compared with the available binding surface in the active site of the protein (423. . .

=> d bib abs 6

L62 ANSWER 6 OF 14 USPATFULL
AN 2001:233298 USPATFULL
TI Nucleic acid affinity columns
IN Lipshutz, Robert J., Palo Alto, CA, United States
Morris, MacDonald S., Felton, CA, United States
Chee, Mark S., Del Mar, CA, United States
Gingeras, Thomas R., Santa Clara, CA, United States
PI US 2001053526 A1 20011220
AI US 2001-910223 A1 20010720 (9)
RLI Division of Ser. No. US 1999-429521, filed on 28 Oct 1999, GRANTED, Pat. No. US 6280950 Division of Ser. No. US 1997-815395, filed on 10 Mar 1997, GRANTED, Pat. No. US 6013440
PRAI US 1996-13231P 19960311 (60) <--
DT Utility
FS APPLICATION
LREP TOWNSEND AND TOWNSEND AND CREW, TWO EMBARCADERO CENTER, EIGHTH FLOOR, SAN FRANCISCO, CA, 94111-3834
CLMN Number of Claims: 40
ECL Exemplary Claim: 1
DRWN 1 Drawing Page(s)
LN.CNT 1762
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides nucleic acid affinity matrices that bear a large number of different nucleic acid affinity ligands allowing the simultaneous selection and removal of a large number of preselected nucleic acids from the sample. Methods of producing such affinity matrices are also provided. In general the methods involve the steps of a) providing a nucleic acid amplification template array comprising a surface to which are attached at least 50 oligonucleotides having different nucleic acid sequences, and wherein each different oligonucleotide is localized in a predetermined region of said surface, the density of said oligonucleotides is greater than about 60 different oligonucleotides per 1 cm.sup.2, and all of said different oligonucleotides have an identical terminal 3' nucleic acid sequence and an identical terminal 5' nucleic acid sequence. b) amplifying said multiplicity of oligonucleotides to provide a pool of amplified nucleic acids; and c) attaching the pool of nucleic acids to a **solid support.**

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 6

L62 ANSWER 6 OF 14 USPATFULL
PRAI US 1996-13231P 19960311 (60) <--
AB . . . of oligonucleotides to provide a pool of amplified nucleic acids; and c) attaching the pool of nucleic acids to a **solid support.**
SUMM . . . be exploited for purification. The process can be used to isolate specific substances such as enzymes, hormones, specific proteins, inhibitors, **antigens**, antibodies, etc. on the basis of the biologic specific interactions with immobilized ligands.
SUMM [0010] The method can further involve attaching the pool of nucleic acids to a **solid support** to form a nucleic acid affinity matrix.
SUMM [0011] The template nucleic acids comprising the amplification template

can be synthesized entirely using light-directed **polymer** synthesis or channel methods. Alternatively the template nucleic acids can be synthesized using a combination of methods. For example, in. . . standard phosphotriester (e.g., phosphoramidite) chemistry. A middle (unique) portion of the template nucleic acids can then be synthesized using light-directed **polymer** synthesis or mechanically-directed synthesis methods. Finally, the 5' segments (subsequences) of the template nucleic acids can be synthesized using phosphotriester. . .

SUMM . . . sample or complementary to a subsequence of the unknown nucleic acid message; and second, attaching the nucleic acids to a **solid support**. The oligonucleotides can be selected by: i) providing a list of all possible oligonucleotides of length K; ii) deleting from. . . from the nucleic acid amplification template arrays described above. In a particularly preferred embodiment, the oligonucleotides are attached to a **solid support** (e.g. glass beads) by a covalent linkage to a biotin which is joined to a streptavidin which is covalently joined to the **solid support**.

SUMM [0024] The term nucleic acid "affinity matrix", as used herein, refers to a **solid support** or gel to which is attached a multiplicity of different oligonucleotides. It is recognized that a nucleic acid template array,. . . do not interfere with subsequent hybridization of attached oligonucleotides. Suitable matrix materials include, but are not limited to paper, glasses, **ceramics**, metals, metalloids, polacryloylmorpholide, various plastics and plastic copolymers such as Nylon.TM., Teflon.TM., polyethylene, polypropylene, poly(4-methylbutene), polystyrene, polystyrene, polystyrene/latex, polymethacrylate, poly(ethylene terephthalate), rayon, nylon, poly(vinyl butyrate), polyvinylidene difluoride (PVDF), **silicones**, polyformaldehyde, cellulose, cellulose acetate, nitrocellulose, and controlled-pore glass (Controlled Pore Glass, Inc., Fairfield, N.J.), aerogels (see, e.g., Ruben et al.,. . .

SUMM . . . for the amplification of nucleic acid pools comprising capture probes that are used either in solution or bound to a **solid support** to provide nucleic acid affinity matrices. Preferred nucleic acid templates additionally include primer binding regions to facilitate amplification. A particularly. . .

SUMM [0032] The terms "nucleic acid" or "nucleic acid molecule" refer to a deoxyribonucleotide or ribonucleotide **polymer** in either single-or double-stranded form, and unless otherwise limited, would encompass known analogs of natural nucleotides that can function in. . .

SUMM . . . in nucleic acid pools) where they may act as blocking probes or where they can be subsequently bound to a **solid support** to produce an affinity matrix.

DETD . . . invention provides a method of preparing pools of nucleic acids and, by attaching the pool(s) of nucleic acids to a **solid support**, a method of preparing nucleic acid affinity matrices. Both the pool of nucleic acids and the affinity matrices comprise a. . .

DETD . . . can be designed from which the capture probes can be amplified. The nucleic acid templates are all attached to a **solid support** thereby forming a "template array" (see FIG. 1, "DNA chip"). In a preferred embodiment, each template nucleic acid is located in a particular preselected region on the **solid support**. Thus, for example, the DNA chip of FIG. 1 shows an array of "rectangles" where each rectangle contains a different. . .

DETD . . . than the number of template molecules used to amplify that species. The amplified nucleic acids are then attached to a **solid support** (e.g. glass or plastic beads) to form an

affinity matrix. The affinity matrix can be arranged or packaged into a. . .

DETD [0057] 4) The capture probes are then attached to a **solid support** (matrix material) to thereby produce an affinity matrix.

DETD . . . nucleic acid templates can be provided free in solution, in a preferred embodiment the templates are themselves bound to a **solid support** forming an amplification template array. In a particularly preferred embodiment, the amplification template arrays of this invention are high density. . .

DETD . . . preferably amplified from a multiplicity of amplification templates, more preferably from a group of templates that comprising a high density **array** of oligonucleotides. Methods of forming **high density arrays** of oligonucleotides, **peptides** and other **polymer** sequences with a minimal number of synthetic steps are known. The oligonucleotide analogue array can be synthesized on a solid. . . See also, Fodor et al., Science, 251, 767-77 (1991) which is incorporated herein by reference. These procedures for synthesis of **polymer** arrays are now referred to as VLSIPS.TM. procedures. Using the VLSIPS.TM. approach, one heterogenous array of **polymers** is converted, through simultaneous coupling at a number of reaction sites, into a different heterogenous array. See, U.S. application Ser.. . .

DETD . . . proceeds using automated phosphoramidite chemistry and chip masking techniques. In one specific implementation, a glass surface is derivatized with a **silane** reagent containing a functional group, e.g., a hydroxyl or amine group blocked by a photolabile protecting group. Photolysis through a. . .

DETD . . . "flow channel" method applied to the compounds and libraries of the present invention can generally be described as follows. Diverse **polymer** sequences are synthesized at selected regions of a substrate or **solid support** by forming flow channels on a surface of the substrate through which appropriate reagents flow or in which appropriate reagents. . .

DETD . . . binding (affinity ligand) regions of the templates. Thus, for example, the first primer binding regions can be synthesized on the **solid support** according to any standard oligonucleotide synthesis method (e.g. standard phosphotriester chemistry). The fmal base added can bear a MenPoc or. . .

DETD . . . can be synthesized in a batch process and the completed primer binding region sequence can then be coupled to the **solid support** forming the amplification template array or to the unique (affinity ligand) region of the templates present in the template array.. . . 3' hydroxyl of one oligonucleotide with the 5' hydroxyl of a second oligonucleotide (or to an activated site on a **solid support** or linker). The linkage can be through the formation of a phosphodiester linkage. Typically this is accomplished by providing one. . .

DETD . . . above-described combinatorial synthetic methods as well as the standard synthetic methods result in the production of oligonucleotides linked to a **solid support** (e.g. a glass slide or controlled pore glass) via a linker. Typically in these methods oligonucleotide synthesis commences by coupling of a nucleotide to a reactive group on a linker which in turn is bound to the **solid support**. The reactive group can be a terminal hydroxyl directly on the **solid support**, or the 3' or 5' hydroxyl of a nucleotide which in turn is bound to the **solid support** either directly or through a linker. Suitable linkers are well known to those of skill in the art. (see, e.g.. . .

DETD . . . with concentrated ammonia). Conversely, where the subsequent amplifications are to be performed with the template nucleic acids

attached to a **solid support**, the linker is not cleaved before amplification. In a preferred embodiment, the amplification is performed with the template oligonucleotides retained on the **solid support**. The amplification template array can then be reused as a template for a number of amplifications and the production of. . .

DETD . . . nucleic acids comprising the template pool can be performed in solution or with the template nucleic acids anchored to a **solid support** (e.g., a glass slide) and thereby forming a template array. In a preferred embodiment, amplification is by polymerase chain reaction. . .

DETD [0156] 3) Attachment of the Amplified Nucleic Acids to a **Solid Support** to Produce an Affinity Matrix.

DETD . . . solid material or gel that does not substantially interfere with hybridization of the oligonucleotides. Suitable matrix materials include paper, glasses, **ceramics**, metals, metalloids, polacryloylmorpholide, various plastics and plastic copolymers such as Nylon.TM., Teflon.TM., polyethylene, polypropylene, poly(4-methylbutene), polystyrene, polystyrene, polystyrene/latex, polymethacrylate, poly(ethylene terephthalate), rayon, nylon, poly(vinyl butyrate), polyvinylidene difluoride (PVDF), **silicones**, polyformaldehyde, cellulose, cellulose acetate, nitrocellulose, and the like. Materials that typically bind nucleic acids (e.g. cellulose) are suitable, however, in. . .

DETD . . . beads, porous beads, crushed particles, membranes, tubing, planar surfaces, etc. Preferred matrix materials are particulate (e.g. beads) thereby providing increased **surface area** for attachment of affinity ligands. Particularly preferred matrix materials can be porous (fenestrated) highly convoluted and/or rugose (e.g. controlled pore. . .

DETD [0160] Methods of attaching oligonucleotides to **solid supports** (matrix materials) are well known to those of skill in the art. For example, in a preferred embodiment, the primers. . . biotin or streptavidin. The amplified nucleic acids will then bear the biotin or streptavidin and can be coupled to a **solid support** bearing avidin (streptavidin) or biotin respectively.

DETD [0161] Alternatively, the nucleic acid can be covalently coupled to the **solid support** either directly via an activated group (e.g. a hydroxyl, a carboxyl) or through a linker that provides reactive moieties that. . .

CLM What is claimed is:

2. The method of claim 1, further comprising the step of attaching said pool of nucleic acids to a **solid support** to form a nucleic acid affinity matrix.

3. The method of claim 2, wherein said amplification template array is synthesized using light-directed **polymer** synthesis.

. . . and said 5' nucleic acid sequences are synthesized using phosphotriester chemistry while the remaining non-identical sequences are synthesized using light-directed **polymer** synthesis.

. . . does not include every possible oligonucleotide having the same length as said oligonucleotides; and ii) attaching said oligonucleotides to a **solid support**.

31. The method of claim 30, wherein said nucleic acid template array is synthesized using light-directed **polymer** synthesis methods.

. . . does not include every possible oligonucleotide having the same

length as said predetermined oligonucleotides; and ii) attaching said oligonucleotides to **solid support** to produce an affinity matrix.

38. The method of claim 41, wherein said nucleic acid template array is synthesized using light-directed **polymer** synthesis methods.

39. The method of claim 34, wherein said oligonucleotides are attached to a said **solid support** by attachment to a biotin which is attached to a streptavidin bound to said **solid support**.

=> d bib abs 7

L62 ANSWER 7 OF 14 USPATFULL
AN 2001:205570 USPATFULL
TI Methods and compositions for amplifying detectable signals in specific binding assays
IN Goldberg, Martin J., Saratoga, CA, United States
Yelagalawadi, Govinda Rao S., San Jose, CA, United States
Tanimoto, Eugene Yuji, Menlo Park, CA, United States
Tran, Huu Minh, Milpitas, CA, United States
Dong, Helin, Palo Alto, CA, United States
Lockhart, David, Mountain View, CA, United States
Ryder, Thomas B., Los Gatos, CA, United States
Warrington, Janet A., Los Altos, CA, United States
Beecher, Jody, San Jose, CA, United States
PA Affymetrix, Inc. (U.S. corporation)
PI US 2001041335 A1 20011115
AI US 2001-776770 A1 20010206 (9)
RLI Continuation of Ser. No. US 1999-276774, filed on 25 Mar 1999, GRANTED, Pat. No. US 6203989
PRAI US 1998-102577P 19980930 (60) <--
DT Utility
FS APPLICATION
LREP Pillsbury Winthrop LLP, Intellectual Property Group, East Tower, Ninth Floor, 1100 New York Avenue, N.W., Washington, DC, 20005-3918
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 2 Drawing Page(s)
LN.CNT 1481
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and compounds are provided for detecting target molecules in a sample using specific binding assays. In particular, methods are provided for detecting a nucleic acid target in a sample. In one embodiment, the method comprises hybridizing a nucleic acid target, comprising a target nucleic acid sequence, to a nucleic acid probe, comprising a probe nucleic acid sequence, wherein the target comprises a binding ligand. The hydridized target is contacted with a receptor comprising multiple sites capable of binding the binding ligand to complex the receptor to the binding ligand, and the receptor is contacted with an amplification reagent, comprising a plurality of the binding ligands, to complex the amplification reagent to the receptor. The presence of the complexed amplification reagent then is detected, for example, by detecting the presence of a detectable label, such as a fluorescent label, for example, on the receptor or the amplification reagent. Optionally, the amplification reagent, comprising a plurality of the binding ligands, is contacted with labeled receptor molecules thereby to complex a plurality of labeled receptor molecules to the amplification reagent, and the labeled receptor molecules complexed to the amplification reagent are detected. This permits the detectable signal to be enhanced and amplified. In one embodiment, the binding ligand is biotin, the receptor is streptavidin, and the amplification reagent is an antibody or a DNA matrix. In another embodiment, an array of different nucleic acid probes immobilized on a surface, each having a defined sequence and location on the surface, may be used in the assays, thus permitting screening and detection of binding of a large number of nucleic acids.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 7

L62 ANSWER 7 OF 14 USPATFULL
PRAI US 1998-102577P 19980930 (60) <--
SUMM . . . of specificity and lack of sensitivity. It is an object of the invention to provide materials for the detection of **polymers**, particularly nucleic acids. It is a particular object of the invention to provide methods and compounds for amplifying labeling signals. . .
SUMM [0011] The amplification reagent may comprise a **polymer**, such as a poly(amino acid) or a polynucleotide. In one embodiment, the amplification reagent may be an antibody, such as. . .
SUMM . . . the nucleic acid probe is immobilized on a surface. The surface may be, for example, Langmuir Blodgett film, glass, germanium, **silicon**, (poly)tetrafluorethylene, polystyrene, gallium arsenide, gallium phosphide, **silicon** oxide, **silicon** nitride, and combinations thereof.
DETD . . . capable of binding the receptor, for example, via non-covalent specific binding interactions. The amplification reagent may comprise, for example, a **polymer**, such as a poly(amino acid) or poly(ester).
DETD . . . to an immunoglobulin molecule or a fragment of an immunoglobulin molecule having the ability to specifically bind to a particular **antigen**. The antibody may be an anti-receptor antibody specific for the receptor used in the assay. Thus, the antibody may be capable of specifically binding the receptor as the **antigen**. Antibodies and methods for their manufacture are well known in the art of immunology. The antibody may be produced, for. . . Fab, Fab', F(ab').sub.2, Facb, Fv, ScFv, Fd, V.sub.H and V.sub.L. Antibodies include but are not limited to single chain antibodies, **chimeric** antibodies, mutants, fusion proteins, humanized antibodies and any other modified configuration of an immunoglobulin molecule that comprises an **antigen** recognition site of the required specificity.
DETD . . . synthetic antibody fragments, cells, cell membranes and moieties therein including cell membrane receptors, and organelles. Examples of ligand-receptor pairs include antibody-**antigen**; lectin-carbohydrate; peptide-cell membrane receptor; protein A-antibody; hapten-antihapten; digoxigenin-anti-digoxigenin; enzyme-cofactor and enzyme-substrate.
DETD [0062] Binding ligands, such as biotins, may be attached to amplification molecules, such as **polymers**, including poly(amino acids), such as antibodies, using methods available in the art. Exemplary methods are disclosed in detail in Bayer. . .
DETD . . . assay using a sulfonate buffer may be conducted with nucleic acid probes immobilized on a solid surface, such as a **silicon** or glass surface. The solid surface may be, for example, coated with a **silane** coating prior to immobilization of the nucleic acid probes. The hybridization assay in a solution comprising a sulfonate buffer may. . .
DETD [0077] Methods for screening using arrays of **polymers**, such as nucleic acids, immobilized on a solid substrate, are disclosed, for example, in U.S. Pat. No. 5,510,270, the disclosure. . . herein. In this method, an array of diverse nucleic acids is formed on a substrate. The fabrication of arrays of **polymers**, such as nucleic acids, on a solid substrate, and methods of use of the arrays in different assays, are described. . . microns or even a small molecule. Such probe arrays may be of the type known as Very Large Scale Immobilized **Polymer** Synthesis (VLSIPS.RTM.). U.S. Pat. No. 5,631,734, the disclosure of which is incorporated herein.

DETD . . . to which arrays of polynucleotides are attached are referred to herein as "biological chips". The substrate may be, for example, **silicon** or glass, and can have the thickness of a microscope slide or glass cover slip. Substrates that are transparent to. . . the disclosure of which is incorporated herein. Other substrates include Langmuir Blodgett film, germanium, (poly)tetrafluorethylene, polystyrene, gallium arsenide, gallium phosphide, **silicon** oxide, **silicon** nitride, and combinations thereof.

DETD . . . the substrate. The nucleic acids of a particular sequence are provided within a predefined region of a substrate, having a **surface area**, for example, of about 1 cm.sup.2 to 10.sup.-10 cm.sup.2. In some embodiments, the regions have areas of less than about. . . exceeding about 400 different nucleic acids/cm.sup.2, wherein each of the different nucleic acids is attached to the surface of the **solid support** in a different predefined region, has a different determinable sequence, and is, for example, at least 4 nucleotides in length.. . .

DETD . . . the disclosure of which is incorporated herein. Methods and systems for detecting a labeled marker on a sample on a **solid support**, wherein the labeled material emits radiation at a wavelength that is different from the excitation wavelength, which radiation is collected. . . .

DETD . . . described herein may be used in a range of applications including biomedical and genetic research and clinical diagnostics. Arrays of **polymers** such as nucleic acids may be screened for specific binding to a target, such as a complementary nucleotide, for example,. . . .

DETD [0088] Gene expression may be monitored by hybridization of large numbers of mRNAs in parallel using **high density arrays** of nucleic acids in **cells**, such as in microorganisms such as yeast, as described in Lockhart et al., Nature Biotechnology, 14:1675-1680 (1996), the disclosure of. . . .

DETD . . . may be used for forming arrays. For example, a computer system may be used to select nucleic acid or other **polymer** probes on the substrate, and design the layout of the array as described in U.S. Pat. No. 5,571,639, the disclosure. . . .

CLM What is claimed is:

. . . The method of claim 19, wherein the surface is selected from the group consisting of Langmuir Blodgett film, glass, germanium, **silicon**, (poly)tetrafluorethylene, polystyrene, gallium arsenide, gallium phosphide, **silicon** oxide, **silicon** nitride, and combinations thereof.

=> d bib abs 8

L62 ANSWER 8 OF 14 USPATFULL
AN 2001:190900 USPATFULL
TI Method for comparing copy number of nucleic acid sequences
IN Fodor, Stephen P. A., Palo Alto, CA, United States
Solas, Dennis W., San Francisco, CA, United States
Dower, William J., Menlo Park, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6309822 B1 20011030
AI US 1996-772376 19961223 (8)
RLI Continuation-in-part of Ser. No. US 1990-670118, filed on 25 Jun 1990, now patented, Pat. No. US 5800992 Continuation-in-part of Ser. No. US 1999-529115, filed on 15 Sep 1999, now patented, Pat. No. US 6040138 Division of Ser. No. US 1993-168904, filed on 15 Dec 1993, now abandoned Continuation of Ser. No. US 1990-624114, filed on 6 Dec 1990, now abandoned Continuation-in-part of Ser. No. US 1989-362901, filed on 7 Jun 1989, now abandoned
PRAI WO 1996-US14839 19960913 <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Zitomer, Stephanie
LREP Pillsbury Winthrop LLP
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 14 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 7686
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides methods for comparing and identifying differences in nucleic acid sequences using a plurality of sequence specific recognition reagents (i.e., probes comprising a nucleic acid complementary to a nucleic acid sequence in collections to be compared) bound to a solid surface.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d kwic 8

L62 ANSWER 8 OF 14 USPATFULL
PRAI WO 1996-US14839 19960913 <--
SUMM . . . genes (e.g., a Northern Blot). In some assay formats, the oligonucleotide probe is tethered, i.e., by covalent attachment, to a **solid support**, and arrays of oligonucleotide probes immobilized on **solid supports** have been used to detect specific nucleic acid sequences in a target nucleic acid.
SUMM The development of VLSIPS.TM. technology provided methods for synthesizing arrays of many different oligonucleotide probes that occupy a very small **surface area**. See U.S. Pat. No. 5,143,854 and PCT patent publication No. WO 90/15070. U.S. patent application Ser. No. 082,937, filed Jun.. . .
SUMM Oligonucleotide arrays for the practice of some embodiments of this invention are, in preferred embodiments, chemically synthesized by parallel immobilized **polymer** synthesis methods, more preferably by light directed **polymer** synthesis methods. Chemically synthesized arrays are advantageous in that probe preparation does not require cloning, a nucleic acid amplification step,. . .
SUMM The terms "nucleic acid" or "nucleic acid molecule" refer to a deoxyribonucleotide or ribonucleotide **polymer** in either

single-or double-stranded form, and unless otherwise limited, would encompass analogs of natural nucleotide that can function in a. . .

DETD . . . about 65,000 or 250,000 or even greater than about 1,000,000 different oligonucleotide probes, preferably in less than 1 cm2 of **surface area**. The oligonucleotide probes range from about 5 to about 50 or about 5 to about 45 nucleotide, more preferably from. . .

DETD . . . more preferably greater than about 100,000, and most preferably greater than about 400,000 different oligonucleotide probes per cm. The small **surface area** of the array (often less than about 10 cm.sup.2, preferably less than about 5 cm.sup.2 more preferably less than about. . .

DETD Methods of forming **high density arrays** of oligonucleotides, **peptides** and other **polymer** sequences with a minimal number of synthetic steps are known. The oligonucleotide analogue array can be synthesized on a solid. . . using, for example, light-directed synthesis techniques. See also, Fodor et al., Science, 251, 767-77 (1991). These procedures for synthesis of **polymer** arrays are now referred to as VLSIPS.TM. procedures. Using the VLSIPS.TM. approach, one heterogenous array of **polymers** is converted, through simultaneous coupling at a number of reaction sites, into a different heterogenous array. See, U.S. application Ser.. . .

DETD . . . proceeds using automated phosphoramidite chemistry and chip masking techniques. In one specific implementation, a glass surface is derivatized with a **silane** reagent containing a functional group, e.g., a hydroxyl or amine group blocked by a photolabile protecting group. Photolysis through a. . .

DETD . . . "flow channel" method applied to the compounds and libraries of the present invention can generally be described as follows. Diverse **polymer** sequences are synthesized at selected regions of a substrate or **solid support** by forming flow channels on a surface of the substrate through which appropriate reagents flow or in which appropriate reagents. . .

DETD . . . preferred embodiment, for which the specific reagents are most easily accessible, the invention is also applicable to analysis of other **polymers**, including polypeptides, carbohydrates, and synthetic **polymers**, including .alpha.-, .beta.-, and .omega.-amino acids, polyurethanes, polyesters, polycarbonates, polyureas, polyamides, polyethyleneimines, polyarylene sulfides, **polysiloxanes**, polyimides, polyacetates, and mixed **polymers**. Various optical isomers, e.g., various D- and L- forms of the monomers, may be used.

DETD . . . prepare substrates on which specific reagents may be either positionally attached or synthesized. In particular, the very large scale immobilized **polymer** synthesis (VLSIPS.TM.) technology allows for the very high density production of an enormous diversity of reagents mapped out in a known matrix pattern on a substrate. These reagents specifically recognize subsequences in a target **polymer** and bind thereto, producing a map of positionally defined regions of interaction. These map positions are convertible into actual features. . .

DETD . . . recognition reagents will often be oligonucleotides which hybridize with fidelity and discrimination to the target sequence. For use with other **polymers**, monoclonal or polyclonal antibodies having high sequence specificity will often be used.

DETD . . . No. 5,498,678). By use of masking technology and photosensitive synthetic subunits, the VLSIPS apparatus allows for the stepwise synthesis of **polymers** according to a positionally defined matrix pattern. Each oligonucleotide probe will be synthesized at known and defined positional locations on. . . 10.sup.2, 10.sup.3

/cm.sup.2, 10.sup.4 /cm.sup.2, 10.sup.5 /cm.sup.2 and up to 10.sup.6 /cm.sup.2 or more. This application discloses methods for synthesizing **polymers** on a **silicon** or other suitably derivatized substrate, methods and chemistry for synthesizing specific types of biological **polymers** on those substrates, apparatus for scanning and detecting whether interaction has occurred at specific locations on the substrate, and various other technologies related to the use of a high density very large scale immobilized **polymer** substrate. In particular, sequencing, fingerprinting, and mapping applications are discussed herein in detail, though related technologies are described in simultaneously. . .

DETD In other embodiments, antibody probes will be generated which specifically recognize particular subsequences found on a **polymer**. Antibodies would be generated which are specific for recognizing a three contiguous amino acid sequence, and monoclonal antibodies may be. . . carbohydrate linkages or sequences will be generated. A similar approach could be used for preparing specific reagents which recognize other **polymer** subunit sequences. These reagents would typically be site specifically localized to a substrate matrix pattern where the regions are closely. . .

DETD Briefly, the binary synthesis strategy refers to an ordered strategy for parallel synthesis of diverse **polymer** sequences by sequential addition of reagents which may be represented by a reactant matrix, and a switch matrix, the product. . .

DETD In particular, this procedure provides a simplified and highly efficient method for saturating all possible sequences of a defined length **polymer**. This masking strategy is also particularly useful in producing all possible oligonucleotide sequence probes of a given length.

DETD . . . described specifically for polynucleotide sequences, similar sequencing, fingerprinting, mapping, and screening procedures can be applied to polypeptide, carbohydrate, or other **polymers**. In particular, the present invention may be used to completely sequence a given target sequence to subunit resolution. This may. . .

DETD . . . the substrate. The data are typically taken over regions substantially smaller than the area in which synthesis of a given **polymer** has taken place. Merely by way of example, if **polymers** were synthesized in squares on the substrate having dimensions of 500 microns by 500 microns, the data may be taken. . . florescence data are taken across the substrate are less than about 1/2 the area of the regions in which individual **polymers** are synthesized, preferably less than 1/10 the area in which a single **polymer** is synthesized, and most preferably less than 1/100 the area in which a single **polymer** is synthesized. Hence, within any area in which a given **polymer** has been synthesized, a large number of fluorescence data points are collected.

DETD The reagents for recognizing the subsequences will usually be specific for recognizing a particular **polymer** subsequence anywhere within a target **polymer**. It is preferable that conditions may be devised which allow absolute discrimination between high fidelity matching and very low levels. . . probes; for polypeptides and carbohydrates, antibodies will be useful reagents. Antibody reagents should also be useful for other types of **polymers**.

DETD This reconstruction process may be applied to **polymers** of virtually any number of possible characters in the alphabet, and for virtually any length sequence to be sequenced, though. . .

DETD For other **polymer** targets, the specific reagents will often be polypeptides. These polypeptides may be protein binding domains from enzymes or other proteins. . . Principles and Practice (2d Ed.) Academic Press, San Diego. Other suitable techniques for in vitro

exposure of lymphocytes to the **antigens** or selection of libraries of antibody binding sites are described, e.g., in Huse et al. (1989) Science 246:1275-1281; and Ward. . .

DETD The antibody specific reagents should be particularly useful for the polypeptide, carbohydrate, and synthetic **polymer** applications. Individual specific reagents might be generated by an automated process to generate the number of reagents necessary to advantageously. . .

DETD . . . the desired matrix pattern of different sequences. Although the binary masking strategy allows for the synthesis of all lengths of **polymers**, the strategy may be easily modified to provide only **polymers** of a given length. This is achieved by omitting steps where a subunit is not attached.

DETD . . . or mapping. For example, it will be desired to determine the spectrum of binding affinities and specificities of cell surface **antigens** with binding by particular antibodies immobilized on the substrate surface, particularly under different interaction conditions. In a related fashion, different. . .

DETD . . . labeling is described, e.g., in Chaplin and Kennedy (1986) Carbohydrate Analysis: A Practical Approach, IRL Press, Oxford. Labeling of other **polymers** will be performed by methods applicable to them as recognized by a person having ordinary skill in manipulating the corresponding **polymer**.

DETD Typically, an **antigen**, or collection of **antigens** are presented to an immune system. This may take the form of synthesized short **polymers** produced by the VLSIPS technology, or by the other synthetic means, or from isolation of natural products. For example, **antigen** for the polypeptides may be made by the VLSIPS technology, by standard peptide synthesis, by isolation of natural proteins with. . .

DETD The **antigen** or collection is presented to an appropriate immune system, e.g., to a whole animal as in a standard immunization protocol,. . .

DETD . . . purified having the desired sequence specificities by isolating the cells producing them. For example, a VLSIPS substrate with the desired **antigens** synthesized thereon may be used to isolate cells with cell surface reagents which recognize the **antigens**. The VLSIPS substrate may be used as an affinity reagent to select and recover the appropriate cells. Antibodies from those. . .

DETD . . . Supernatants from a large population of producing cells may be passed over a VLSIPS substrate to bind to the desired **antigens** attached to the substrate. When a sufficient density of antibody molecules are attached, they may be removed by an automated. . .

DETD In one particular embodiment, a VLSIPS substrate, e.g., with a large plurality of fingerprint **antigens** attached thereto, is used to isolate antibodies from a supernatant of a population of cells producing antibodies to the **antigens**. Using the substrate as an affinity reagent, the antibodies will attach to the appropriate positionally defined **antigens**. The antibodies may be carefully removed therefrom, preferably by an automated system which retains their homogeneous specificities. The isolated antibodies. . .

DETD . . . steps for synthesizing a specific sequence thereon. Then, by successive VLSIPS cycles, each of the antibodies attached to the defined **antigen** regions can have a defined oligonucleotide synthesized thereon and corresponding in area to the region of the substrate having each **antigen** attached. These defined oligonucleotides will be useful as targeting reagents to attach those antibodies possessing the same target sequence specificity at defined positions on a new substrate, by virtue of having bound to the **antigen** region, to a new VLSIPS substrate having the complementary target oligonucleotides positionally located on it. In this fashion, a VLSIPS substrate having

the desired **antigens** attached thereto can be used to generate a second VLSIPS substrate with positionally defined reagents which recognize those **antigens**.

DETD The selected **antigens** will typically be selected to be those which define particular functionalities or properties, so as to be useful for fingerprinting. . .

DETD . . . sequence recognition reagent. For example, the sequence specific reagents having a separate additional sequence recognition segment (usually of a different **polymer** from the target sequence) can be directed to target oligonucleotides attached to the substrate. By use of non-natural targeting reagents,. . . isomers of nucleotides may be useful unnatural reagents subject to similar chemistry, but incapable of interfering with the natural biological **polymers**. See also, U.S. Ser. No. 07/626,730, which is hereby incorporated herein by reference.

DETD . . . reagents are known, see, e.g., Dattagupta et al. (1985) U.S. Pat. No. 4,542,102 and (1987) "Coupling of nucleic acids to **solid support** by photochemical methods," U.S. Pat. No.4,713,326, each of which is hereby incorporated herein by reference. Similar linkages for attachment of. . .

DETD . . . of specific data. In one embodiment, the probes used are selected to be of sufficiently high resolution to measure the **antigens** of the major histo compatibility complex. It might even be possible to provide transplantation matching data in a linear stream. . .

DETD Besides polynucleotide applications, the fingerprinting analysis may be applied to other **polymers**, especially polypeptides, carbohydrates, and other **polymers**, both organic and inorganic. Besides using the fingerprinting method for analyzing a particular **polymer**, the fingerprinting method may be used to characterize various samples. For example, a cell or population of cells may be tested for their expression of specific **antigens** or their mRNA sequence content. For example, a T-cell may be classified by virtue of its combination of expressed surface **antigens**. With specific reagents which interact with these **antigens**, a cell or a population of cells or a lysed cell may be exposed to a VLSIPS substrate. The biological. . .

DETD In a similar manner, the **antigenic** determinants found on a protein may very well define the cell class. For example, immunological T-cells are distinguishable from B-cells because, in part, the cell surface **antigens** on the cell types are distinguishable. Different T-cell subclasses can be also distinguished from one another by whether they contain particular T-cell **antigens**. The present invention provides the possibility for high resolution testing of many different interactions simultaneously, and the definition of new. . .

DETD . . . found in the blood. For example, a cancerous condition may be indicated by a combination of expression of various soluble **antigens** found in the blood along with a high number of various cellular **antigens** found on lymphocytes and/or particular cell degradation products. With a substrate as provided herein, a large number of different features. . . tests may be limited by the extent of statistical correlation with a particular condition rather than with the number of **antigens** or interactions which are tested. The present invention provides the means to generate this large universe of possible reagents and. . .

DETD . . . be utilized and a cell class may be defined by a combination of its expressed mRNA, its carbohydrate expression, its **antigens**, and other properties. This fingerprinting should be useful in determining the physiological state of a cell or population of cells.

DETD . . . a cell type whose function or properties are defined by the reagents attachable to a VLSIPS substrate, such as cellular **antigens**, these structural manifestations of function may be used to sort cells to generate a relatively homogeneous population of that class. . .

DETD The invention will also find use in detecting changes, both genetic and **antigenic**, e.g., in a rapidly "evolving" protozoa infection, or similarly changing organism.

DETD The use of the present invention for mapping parallels its use for fingerprinting and sequencing. Where a **polymer** is a linear molecule, the mapping provides the ability to locate particular segments along the length of the **polymer**. Branched **polymers** can be treated as a series of individual linear **polymers**. The mapping provides the ability to locate, in a relative sense, the order of various subsequences. This may be achieved. . .

DETD . . . coupled with some indication of the location of the interaction. The interaction is mapped in some manner to the physical **polymer** sequence. Some means for determining the relative positions of different probes is performed. This may be achieved by synthesis of. . .

DETD . . . be randomly positioned at various locations on the substrate. However, the relative positions of the various reagents in the original **polymer** may be determined by using short fragments, e.g., individually, as target molecules which determine the proximity of different probes. By an automated system of testing each different short fragment of the original **polymer**, coupled with proper analysis, it will be possible to determine which probes are adjacent one another on the original target. . .

DETD . . . in this mapping embodiment, antibody reagents may also be very useful. In the same way that polypeptide sequencing or other **polymers** may be sequenced by the reagents and techniques described in the sequencing section and fingerprinting section, the mapping embodiment may. . .

DETD . . . may be measured using fingerprinting type technology. Thus, the mapping may be along a temporal dimension rather than along a **polymer** dimension. The mapping or fingerprinting embodiments may also be used in determining the genetic rearrangements which may be genetically important,. . .

DETD As originally indicated in the parent filing of VLSIPS.TM., the production of a high density plurality of spatially segregated **polymers** provides the ability to generate a very large universe or repertoire of individually and distinct sequence possibilities. As indicated above,. . .

DETD . . . stage of a cell, or population of cells, can be dependent upon the expression of particular messenger RNAs or cellular **antigens** . The screening procedures provided allow for high resolution definition of new classes of cells. In addition, the temporal development of. . .

DETD . . . to select those cells containing or expressing the critical markers. Alternatively, the expression of those sequences may result in specific **antigens** which may also be used in defining cell classes and sorting those cells away from others. In this way, for. . .

DETD In an alternative embodiment, a plurality of **antigens** or specific binding proteins attached to the substrate may be used to define particular cell types. For example, subclasses of T-cells are defined, in part, by the combination of expressed cell surface **antigens**. The present invention allows for the simultaneous screening of a large plurality of different **antigens** together. Thus, higher resolution classification of different T-cell subclasses becomes possible and, with the definitions and functional differences

which correlate with those **antigenic** or other parameters, the ability to purify those cell types becomes available. This is applicable not only to T-cells, but. . .

DETD . . . a sufficiently large population allows detailed statistical analysis to be made, thereby correlating particular medical conditions with particular markers, typically **antigenic** or genetic. Tumor specific **antigens** will be identified using the present invention.

DETD . . . instrumentation described therein is directly applicable to the applications used here. In particular, the apparatus comprises a substrate, typically a **silicon** containing substrate, on which positions on the surface may be defined by a coordinate system of positions. These positions can. . .

DETD The density of reagents attached to a **silicon** substrate may be varied by standard procedures. The **surface area** for attachment of reagents may be increased by modifying the **silicon** surface. For example, a matte surface may be machined or etched on the substrate to provide more sites for attachment. . . particular reagents. Another way to increase the density of reagent binding sites is to increase the derivitization density of the **silicon**. Standard procedures for achieving this are described, below.

DETD . . . appropriate sequence of photo-exposure steps at appropriate times with appropriate masks and with appropriate reagents, the substrates can have known **polymers** synthesized at positionally defined regions on the substrate. Methods for synthesizing various substrates are described in U.S. Ser. No. 07/492,462. . .

DETD In another embodiment, colony or phage plaque transfer of biological **polymers** may be transferred directly onto a **silicon** substrate. For example, a colony plate may be transferred onto a substrate having a generic oligonucleotide sequence which hybridizes to. . .

DETD . . . hybridization as a means to fingerprint a sample. This may be used in a nucleic acid, as well as other **polymer** embodiments. For example, fingerprinting to a high degree of specificity of sequence matching may be used for identifying highly similar. . .

DETD . . . be used to identify cell markers, e.g., proteins, usually on the cell surface, but intracellular markers may also be used. **Antigens** which are extracellularly expressed are preferred so cell lysis is unnecessary in the screening, but intracellular markers may also be. . . be used for determining T-cell classes or perhaps even to generate classification schemes for such proteins as major histocompatibility complex **antigens**. Thus, the ability to make these substrates allows both the generation of reagents which will be used for defining subclasses. . .

DETD In addition to cell classification defined by such a combination of properties, typically expression of extracellular **antigens**, the present invention also provides the means for isolating homogeneous population of cells. Once the **antigenic** determinants which define a cell class have been identified, these **antigens** may be used in a sequential selection process to isolate only those cells which exhibit the combination of defining structural. . .

DETD For example, the specificity of antibody/**antigen** interaction may depend upon such parameters as pH, salt concentration, ionic composition, solvent composition, detergent composition and concentration, and chaotropic. . .

DETD . . . the theoretical and mathematical manipulations necessary for data analysis of other linear molecules, such as polypeptides, carbohydrates, and various other **polymers** are conceptually similar. Simple branching **polymers** will usually also be sequencable using similar technology. However, where there is branching,

it may be desired that additional recognition. . . of appropriate specific reagents which would be generated by methods similar to those used to produce specific reagents for linear **polymers**.

DETD . . . an appropriate substrate may involve either mechanical or automated procedures. The standard VLSIPS automated procedure involves synthesizing oligonucleotides or short **polymers** directly on the substrate. In various other embodiments, it is possible to attach separately synthesized reagents onto the matrix in. . .

DETD Besides polynucleotide sequencing, the present invention also provides means for sequencing other **polymers**. This includes polypeptides, carbohydrates, synthetic organic **polymers**, and other **polymers**. Again, the sequencing may be either verification or de novo.

DETD . . . environments. For example, it will be useful in determining the genetic sequence of particular markers in various individuals. In addition, **polymers** may be used as markers or for information containing molecules to encode information. For example, a short polynucleotide sequence may. . . may be encoded. Production lots of organic compounds such as benzene or plastics may be encoded with a short molecule **polymer**. Food stuffs may also be encoded using similar marking molecules. Even toxic waste samples can be encoded determining the source. . .

DETD As indicated above, **polymers** may be used to encode important information on source and batch and supplier. This is described in greater detail, e.g.,. . .

DETD Thus, the present invention provides a powerful tool and the means for performing sequencing, fingerprinting, and mapping functions on **polymers**. Although most easily and directly applicable to polynucleotides, polypeptides, carbohydrates, and other sorts of molecules can be advantageously utilized using. . .

DETD . . . The just-described moving structure is also referred to herein as dispensing means for moving the dispenser into engagement with a **solid support**, for dispensing a known volume of fluid on the support.

DETD . . . an x-y plane to position the dispenser at a selected deposition position, as will be described. The support is a **polymer**, glass, or other solid-material support having a surface.

DETD . . . covalently attached charged groups. On such surface described below is a glass surface having an absorbed layer of a polycationic **polymer**, such as poly-1-lysine.

DETD . . . relatively hydrophobic character, i.e., one that causes aqueous medium deposited on the surface to bead. A variety of known hydrophobic **polymers**, such as polystyrene, polypropylene, or polyethylene have desired hydrophobic properties, as do glass and a variety of lubricant or other. . .

DETD . . . is desired to first rehydrate the droplets containing the analyte reagents to allow for more time for adsorption to the **solid support**. It is also possible to spot out the analyte reagents in a humid environment so that droplets do not dry. . .

DETD In another aspect, the invention includes an automated apparatus for forming an array of analyte-assay regions on a **solid support**, where each region in the array has a known amount of a selected, analytespecific reagent. A dispenser device in the. . .

DETD This section describes embodiments of a substrate having a microarray of biological **polymers** carried on the substrate surface. Subsection A describes a multi cell substrate, each cell of which contains a microarray, and. . . a porous surface. Subsection B describes a microarray of distinct polynucleotides bound on a glass slide coated with a polycationic **polymer**.

DETD . . . and 1 and 50 mm in length. The substrate includes a water-impermeable backing, such as a glass slide or rigid **polymer** sheet. Formed on the surface of the backing is a water-permeable film. The film is formed of a porous membrane material, such as nitrocellulose membrane, or a porous web material, such as a nylon, polypropylene, or PVDF porous **polymer** material. The thickness of the film is preferably between about 10 and 1000 .mu.m. The film may be applied to. . .

DETD The grid lines are formed on the substrate by laying down an uncured or otherwise flowable resin or **elastomer** solution in an array grid, allowing the material to infiltrate the porous film down to the backing, then curing or. . .

DETD One preferred material for the grid is a flowable **silicone** available from Loctite Corporation. The barrier material can be extruded through a narrow syringe e.g., 22 gauge) using air pressure or mechanical pressure. The syringe is moved relative to the **solid support** to print the barrier elements as a grid pattern. The extruded bead of **silicone** wicks into the pores of the **solid support** and cures to form a shallow waterproof barrier separating the regions of the **solid support**.

DETD . . . can be a wax-based material or a thermoset material such as epoxy. The barrier material can also be a UV-curing **polymer** which is exposed to UV light after being printed onto the **solid support**. The barrier material may also be applied to the **solid support** using printing techniques such as silk-screen printing. The barrier material may also be a heat-seal stamping of the porous **solid support** which seals its pores and forms a water-impervious barrier element. The barrier material may also be a shallow grid which is laminated or otherwise adhered to the **solid support**.

DETD In addition to plastic-backed nitrocellulose, the **solid support** can be virtually any porous membrane with or without a non-porous backing. Such membranes are readily available from numerous vendors. . .

DETD In an alternative embodiment, the **solid support** can be of a non-porous material. The barrier can be printed either before or after the microarray of biomolecules is printed on the **solid support**.

DETD In a preferred embodiment, each microarray contains about 10.sup.3 distinct polynucleotide or polypeptide biopolymers per **surface area** of less than about 1 cm.sup.2. Also in a preferred embodiment, the biopolymers in each microarray region are present in. . .

DETD . . . about 50 bp, i.e., substantially longer than oligonucleotides which can be formed in high-density arrays by schemes involving parallel, step-wise **polymer** synthesis on the array surface.

DETD . . . loaded onto each cell. The solution will spread to cover the entire microarray and stop at the barrier elements. The **solid support** is then incubated in a humid chamber at the appropriate temperature as required by the assay.

DETD . . . kept properly hydrated by the water vapor in the humid chamber. At the conclusion of the incubation step, the entire **solid support** containing the numerous microarrays is rinsed quickly enough to dilute the assay reagents so that no significant cross contamination occurs. The entire **solid support** is then reacted with detection reagents if needed and analyzed using standard calorimetric, radioactive or fluorescent detection means. All processing and detection steps are performed simultaneously to all of the microarrays on the **solid support** ensuring uniform assay conditions for all of the microarrays on the **solid**

support.

DETD The substrate includes a glass substrate having formed on its surface, a coating of a polycationic **polymer**, preferably a cationic polypeptide, such as polylysine or polyarginine. Formed on the polycationic coating is a microarray of distinct polynucleotides,. . .

DETD The slide is coated by placing a uniform-thickness film of a polycationic **polymer**, e.g., poly-1-lysine, on the surface of a slide and drying the film to form a dried coating. The amount of polycationic **polymer** added is sufficient to form at least a monolayer of **polymers** on the glass surface. The **polymer** film is bound to surface via electrostatic binding between negative **silyl**-OH groups on the surface and charged amine groups in the **polymers**. Poly-1-lysine coated glass slides may be obtained commercially, e.g., from Sigma Chemical Co. (St. Louis, Mo.).

DETD In a preferred embodiment, each microarray contains at least 103 distinct polynucleotide or polypeptide biopolymers per **surface area** of less than about 1 cm.sup.2. In one embodiment, the microarray contains 400 regions in an area of about 16. . .

DETD . . . hybridized to the 96 individual arrays with each assay performed in 100 microliters of hybridization solution. The approximately 1" thick **silicone** rubber barrier elements between individual arrays prevent cross contamination of the patient samples by sealing the pores of the nitrocellulose and by acting as a physical barrier between each microarray. The **solid support** containing all 96 microarrays assayed with the 96 patient samples is incubated, rinsed, detected and analyzed as a single sheet. . .

DETD . . . immobilized as the array elements and each array is hybridized with a different mutated allele or genetic marker. The gridded **solid support** can also be used for parallel non-DNA ELISA assays. Furthermore, the invention allows for the use of all standard detection. . .

DETD In addition to the genetic applications listed above, arrays of whole cells, peptides, enzymes, antibodies, **antigens**, receptors, ligands, phospholipids, **polymers**, drug cogener preparations or chemical substances can be fabricated by the means described in this invention for large scale screening. . .

DETD . . . individual arrays for performing mass screenings for genetic research and diagnostic applications. Numerous microarrays can be fabricated on the same **solid support** and each microarray reacted with a different DNA probe while the **solid support** is processed as a single sheet of material.

=> d bib abs 9

L62 ANSWER 9 OF 14 USPATFULL
AN 2001:178805 USPATFULL
TI Expression monitoring for gene function identification
IN Mack, David H., Menlo Park, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6303301 B1 20011016
AI US 1998-86285 19980529 (9)
RLI Continuation-in-part of Ser. No. WO 1998-US1206, filed on 12 Jan 1998
PRAI US 1997-35327P 19970113 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Jones, W. Gary; Assistant Examiner: Forman, B J.
LREP Banner & Witcoff, Ltd.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1
DRWN 24 Drawing Figure(s); 21 Drawing Page(s)
LN.CNT 2680
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides methods, compositions and apparatus for mapping the regulatory relationship among genes by massive parallel monitoring gene expression. In some embodiments, mutations in the up-stream regulatory genes are detected by monitoring the change in down-stream gene expression. Similarly, the function of a specific mutation in a up-stream gene is determined by monitoring the down-stream gene expression. In addition, regulatory function of a target gene can be determined by monitoring the expression of a large number of down-stream genes. The invention also provides specific embodiments for detecting p53 functional homozygous and heterozygous mutations and for determining the function of p53 mutations.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 10

L62 ANSWER 10 OF 14 USPATFULL
AN 2001:142092 USPATFULL
TI Nucleic acid affinity columns
IN Lipshutz, Robert J., Palo Alto, CA, United States
Morris, MacDonald S., San Jose, CA, United States
Chee, Mark S., Palo Alto, CA, United States
Gingeras, Thomas R., Encinitas, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6280950 B1 20010828
AI US 1999-429521 19991028 (9)
RLI Continuation of Ser. No. US 1997-815395, filed on 10 Mar 1997, now patented, Pat. No. US 6013440
PRAI US 1996-13231P 19960311 (60) <--
DT Utility
FS GRANTED
EXNAM Primary Examiner: Horlick, Kenneth R.
LREP Townsend and Townsend and Crew LLP
CLMN Number of Claims: 11
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1621
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides nucleic acid affinity matrices that bear a large number of different nucleic acid affinity ligands allowing the simultaneous selection and removal of a large number of preselected nucleic acids from the sample. Methods of producing such affinity matrices are also provided. In general the methods involve the steps of a) providing a nucleic acid amplification template array comprising a surface to which are attached at least 50 oligonucleotides having different nucleic acid sequences, and wherein each different oligonucleotide is localized in a predetermined region of said surface, the density of said oligonucleotides is greater than about 60 different oligonucleotides per 1 cm.sup.2, and all of said different oligonucleotides have an identical terminal 3' nucleic acid sequence and an identical terminal 5' nucleic acid sequences; b) amplifying said multiplicity of oligonucleotides to provide a pool of amplified nucleic acids; and c) attaching the pool of nucleic acids to a **solid support**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 11

L62 ANSWER 11 OF 14 USPATFULL
AN 2001:40204 USPATFULL
TI Methods and compositions for amplifying detectable signals in specific binding assays
IN Goldberg, Martin J., Saratoga, CA, United States
Yelagalawadi, Govinda Rao S., San Jose, CA, United States
Tanimoto, Eugene Yuji, Menlo Park, CA, United States
Tran, Huu Minh, Milpitas, CA, United States
Dong, Helin, Palo Alto, CA, United States
Lockhart, David, Mountain View, CA, United States
Ryder, Thomas B., Los Gatos, CA, United States
Warrington, Janet A., Los Altos, CA, United States
Beecher, Jody, San Jose, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6203989 B1 20010320
AI US 1999-276774 19990325 (9)
PRAI US 1998-102577P 19980930 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Jones, W. Gary; Assistant Examiner: Taylor, Janell E.
LREP McGarrigle, Philip L.
CLMN Number of Claims: 35
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1478
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods and compounds are provided for detecting target molecules in a sample using specific binding assays. In particular, methods are provided for detecting a nucleic acid target in a sample. In one embodiment, the method comprises hybridizing a nucleic acid target, comprising a target nucleic acid sequence, to a nucleic acid probe, comprising a probe nucleic acid sequence, wherein the target comprises a binding ligand. The hydridized target is contacted with a receptor comprising multiple sites capable of binding the binding ligand to complex the receptor to the binding ligand, and the receptor is contacted with an amplification reagent, comprising a plurality of the binding ligands, to complex the amplification reagent to the receptor. The presence of the complexed amplification reagent then is detected, for example, by detecting the presence of a detectable label, such as a fluorescent label, for example, on the receptor or the amplification reagent. Optionally, the amplification reagent, comprising a plurality of the binding ligands, is contacted with labeled receptor molecules thereby to complex a plurality of labeled receptor molecules to the amplification reagent, and the labeled receptor molecules complexed to the amplification reagent are detected. This permits the detectable signal to be enhanced and amplified. In one embodiment, the binding ligand is biotin, the receptor is streptavidin, and the amplification reagent is an antibody or a DNA matrix. In another embodiment, an array of different nucleic acid probes immobilized on a surface, each having a defined sequence and location on the surface, may be used in the assays, thus permitting screening and detection of binding of a large number of nucleic acids.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 12

L62 ANSWER 12 OF 14 USPATFULL
AN 2000:84038 USPATFULL
TI Chemical amplification for the synthesis of patterned arrays
IN Beecher, Jody E., Mountain View, CA, United States
Goldberg, Martin J., San Jose, CA, United States
McGall, Glenn H., Mountain View, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6083697 20000704
AI US 1997-969227 19971113 (8)
PRAI US 1996-30826P 19961114 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Celsa, Bennett; Assistant Examiner: Ricigliano, Joseph W.
LREP Banner & Witcoff, Ltd.
CLMN Number of Claims: 18
ECL Exemplary Claim: 1
DRWN 8 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1295
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Radiation-activated catalysts (RACs), autocatalytic reactions, and protective groups are employed to achieve a highly sensitive, high resolution, radiation directed combinatorial synthesis of pattern arrays of diverse **polymers**. When irradiated, RACs produce catalysts that can react with enhancers, such as those involved in autocatalytic reactions. The autocatalytic reactions produce at least one product that removes protecting groups from synthesis intermediates. This invention has a wide variety of applications and is particularly useful for the solid phase combinatorial synthesis of **polymers**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 13

L62 ANSWER 13 OF 14 USPATFULL
AN 2000:4603 USPATFULL
TI Nucleic acid affinity columns
IN Lipshutz, Robert J., Palo Alto, CA, United States
Morris, MacDonald S., San Jose, CA, United States
Chee, Mark S., Palo Alto, CA, United States
Gingeras, Thomas R., Encinitas, CA, United States
PA Affymetrix, Inc., Santa Clara, CA, United States (U.S. corporation)
PI US 6013440 20000111
AI US 1997-815395 19970310 (8)
PRAI US 1996-13231P 19960311 (60) <--
DT Utility
FS Granted
EXNAM Primary Examiner: Horlick, Kenneth R.
LREP Townsend & Townsend & Crew
CLMN Number of Claims: 16
ECL Exemplary Claim: 1
DRWN 1 Drawing Figure(s); 1 Drawing Page(s)
LN.CNT 1654
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention provides nucleic acid affinity matrices that bear a large number of different nucleic acid affinity ligands allowing the simultaneous selection and removal of a large number of preselected nucleic acids from the sample. Methods of producing such affinity matrices are also provided. In general the methods involve the steps of a) providing a nucleic acid amplification template array comprising a surface to which are attached at least 50 oligonucleotides having different nucleic acid sequences, and wherein each different oligonucleotide is localized in a predetermined region of said surface, the density of said oligonucleotides is greater than about 60 different oligonucleotides per 1 cm.sup.2, and all of said different oligonucleotides have an identical terminal 3' nucleic acid sequence and an identical terminal 5' nucleic acid sequence. b) amplifying said multiplicity of oligonucleotides to provide a pool of amplified nucleic acids; and c) attaching the pool of nucleic acids to a **solid support**.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d bib abs 14

L62 ANSWER 14 OF 14 USPATFULL
AN 93:16786 USPATFULL
TI Removal of cells from an aqueous suspension
IN Thomson, Alan R., Beaconsfield, England
Stickley, Frances L., Kings Langley, England
Clark, Stephen E., Aylesbury, England
Daiss, John L., Rochester, NY, United States
PA Eastman Kodak Company, Rochester, NY, United States (U.S. corporation)
PI US 5191068 19930302
WO 9007715 19900712
AI US 1990-571619 19900904 (7)
WO 1990-GB12 19900104
19900904 PCT 371 date
19900904 PCT 102(e) date
PRAI GB 1989-252 19890106 <--
DT Utility
FS Granted
EXNAM Primary Examiner: Cashion, Jr., Merrell C.; Assistant Examiner: Rozycki, Andrew G.
LREP Wells, Doreen M.
CLMN Number of Claims: 3
ECL Exemplary Claim: 1
DRWN 4 Drawing Figure(s); 2 Drawing Page(s)
LN.CNT 390
AB A method of removing an **antigenic** substance from a fluid comprises

(1) forming a ternary complex by the interaction of

(a) the **antigenic** substance,

(b) a first antibody which contains a kappa chain and which binds to the **antigenic** substance, and

(c) a second antibody which binds to the kappa chain of the first antibody, said second antibody being immobilized on a solid phase carrier, and

(2) separating the fluid from the solid phase carrier.

=> d kwic 14

L62 ANSWER 14 OF 14 USPATFULL
PRAI GB 1989-252 19890106 <--
AB A method of removing an **antigenic** substance from a fluid comprises
AB (a) the **antigenic** substance,
AB (b) a first antibody which contains a kappa chain and which binds to the **antigenic** substance, and
SUMM The invention relates to a method of removing an **antigenic** substance from a fluid. As used herein, the term **antigenic** substance refers broadly to substances to which antibodies can be produced.
SUMM Affinity separation and purification techniques are known in which an immobilised antibody is used to selectively remove an **antigenic**

substance from a biological fluid. For example, U.K. Patent Application No. 2 135 676 describes a process for producing highly. . .

SUMM . . . and purification of cell sub-types has been carried out using an antibody affinity chromatography process. In such a process, the **antigenic** substance is a surface component of the cells to be removed.

SUMM The invention provides a method of removing an **antigenic** substance from a fluid which method comprises

SUMM (a) the **antigenic** substance,

SUMM (b) a first antibody which contains a kappa chain and which binds to the **antigenic** substance, and

DETD In a preferred embodiment of the invention the fluid is contacted with the first antibody to form an antibody:**antigen** binary complex with the **antigenic** substance and is subsequently contacted with the immobilised second antibody to form the ternary complex.

DETD The method of the invention may be used in respect of a wide variety of **antigenic** substances. Examples of such substances include haptens, hormones, allergens, viruses, bacteria, toxins, some drugs and proteins.

DETD The **antigenic** substance removed from a fluid by the method of the invention may be recovered by elution from the solid phase. . .

DETD . . . impervious support sheet adapted to receive the second antibody wherein the support sheet has adhered thereto a layer comprising a **polymer** having at its surface functional groups which are directly or indirectly reactive with the second antibody.

DETD . . . element may be formed from a variety of materials. For example, a suitable material may be a metal, glass or **polymer**. Many polymeric materials which can be formed into a sheet or film are suitable including, for example, cellulose ethers or. . .

DETD The **polymer** layer on which the second antibody is to be immobilised may be present as an activated **polymer** layer i.e. containing functional groups which will react directly with the antibody. Alternatively, it may be present as an activatable **polymer** layer which is subsequently activated by treatment with an activating agent. The activating agent may convert a functional group of the activatable **polymer** into a functional group capable of reaction with the antibody or it may be a coupling agent which becomes attached to the **polymer** by reaction with a functional group of the activatable **polymer**.

DETD Suitable **polymers** may be derived from monomers such as ethylenically unsaturated hydroxy group-containing monomers e.g. hydroxyethyl methacrylate (HEMA), ethylenically unsaturated oxirane group-containing. . .

DETD Preferably, the activated or activatable **polymer** is substantially hydrophilic. Particularly suitable chemical groups which confer hydrophilicity on the **polymer** include hydroxyl, amino, carboxyl and thiol groups.

DETD In order to minimise the problems associated with the use of porous materials, the activated or activatable **polymer** layer may be substantially non-porous. If the activated or activatable **polymer** layer is porous, it is preferred that the pores are sufficiently small to exclude the entry into the layer of the second antibody and the **antigenic** substance to be removed. Preferably, the activated **polymer** layer is substantially non-swellable.

DETD For ease of manufacture, it is preferred that the activatable or activated **polymer** is solvent-coatable e.g. coatable from solution in water and/or an organic solvent. In this way, conventional coating machinery including, for. . .

DETD Preferably, the activatable or activated **polymer** layer

constitutes a continuous layer over the support.

DETD The thickness of the activated **polymer** layer will depend upon such factors as the particular **polymer** employed. Since, in a preferred embodiment, the interaction between the second antibody and the labelled **antigenic** substance to be removed takes place predominantly at the surface of the layer, it need only be sufficiently thick to. . . provide adequate attachment of the ligand to the support sheet. By way of example, the dry thickness of the activated **polymer** layer may be from 5 to 100 .mu.m, more preferably from 10 to 50 .mu.m.

DETD Adequate adhesion between the activated **polymer** layer and the support sheet may be obtained by appropriate selection of the two materials involved. Alternatively, adhesion may be. . . a subbing layer or by subjecting the support sheet to a corona discharge or RF plasma treatment before applying the **polymer** layer.

DETD A layer of activated **polymer** may be provided on each side of the support sheet.

DETD Various methods may be employed in order to maximise the **surface area** of the activated or activatable **polymer** layer relative to the **surface area** of the support sheet. In one such method, the layer contains inert particulate material which raises the surface of the. . . The particulate material may be in the form of beads. Suitable materials from which the particles may be formed include **polymers** and glass.

DETD The activated or activatable **polymer** layer may contain particulate material which acts as spacer means i.e. the particulate material provides the means whereby an element. . . another part of the same element held against it. The particulate material may be held chemically on or within the **polymer** coating. Preferably, the particulate material comprises particles of substantially uniform shape and dimension. For many applications, it is desirable that. . .

DETD As described above, the particulate material may take a variety of forms including, for example, beads of **polymer** of glass. The dimension of the particles which determines the degree of spacing they provide will depend on such factors as the separation distance required between contiguous elements and the thickness of the activated **polymer** layer. Substantially spherical beads of an inert material all having substantially the same diameter within the range from 20 to. . .

DETD . . . feature of the particulate spacer means described above is that it is possible to coat the particulate material with the **polymer** layer. In this way, an element having integral spacer means is produced. By simply preparing a homogeneous coating composition comprising the **polymer** or monomers from which the **polymer** layer is formed and the particulate material, the particles will be uniformly distributed over the coated layer thereby ensuring uniform. . .

DETD . . . carrier element for use in the invention. The element comprises a support sheet 10 coated with a layer of a **polymer** 11 having the second antibody (not shown) covalently bound to the surface thereof. Beads 12 incorporated in the layer 11. . .

DETD The solution was stirred at 50.degree. C. for 17 hours. Nitrogen was bubbled through the solution throughout this period. The **polymer** was recovered by precipitation into an excess of diethyl ether and dried in a desiccator. (Yield=74.9 g).

DETD 2. Coating the **Polymer**

DETD A coating solution was prepared consisting of 10% w/w of the above **polymer** in 100% dimethylformamide plus 10% w/w tetrabutyl ammonium hydroxide/**polymer**. 100 .mu.m silica-coated styrene beads were incorporated in suspension in the solution as spacer beads.

DETD Samples of the coated **polymer** were activated by treatment with

a 4% divinylsulphone solution in 0.5M sodium bicarbonate, pH 11. Rat anti-mouse K-chain monoclonal antibody at 0.8 mg/ml was coupled to the activated **polymer** coatings in 0.1M sodium bicarbonate, 0.5M sodium chloride solution at pH 8. The rat anti-mouse K-chain antibody was purified from. . .

DETD A total of 3.1.times.10.sup.7 Jurkat cells (5.2.times.10.sup.6 cells/ml) were labelled with a mouse monoclonal antibody against the T cell surface **antigen** CD2. The antibody was obtained from Becton Dickinson Ltd., (Anti-Leu-5b, catalogue No. 7590). The antibody was added to the cells. . .

DETD The **polymer** coatings to which OX-20 was coupled were incubated with the suspension of the labelled cells. The coatings were subsequently washed with PBS and examined **microscopically**. The coatings showed a good even coverage of bound **cells** at **high density**.

DETD . . . coating were incubated with non-antibody labelled cells. Subsequent microscopic examination revealed that virtually no cells had become bound to the **polymer**.

CLM What is claimed is:

. . . the interaction of (a) the cells, (b) a first antibody which contains a kappa chain and which binds to an **antigenic** surface component on the cells, and (c) a second antibody which binds to the kappa chain of the first antibody,. . .

. . . 2. A method according to claim 1 wherein the acqueous suspension is contacted with the first antibody to form an antibody:**antigen** binary complex with the **antigenic** substance and is subsequently contacted with the bound second antibody to form the ternary complex.

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